BEFORE THE

UNITED STATES DEPARTMENT OF DEFENSE

Washington, D.C.

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In the Matter of: :

ARMED FORCES EPIDEMIOLOGICAL BOARD :

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The above-entitled matter came on for meeting, pursuant to Notice before Dr. Gerald F. Fletcher and Colonel Vicky Fogelman, Moderators, at Walter Reed Army Institute of Research, Building 40, Sternberg Auditorium, Washington, D.C. on Thursday, December 12, 1996 at 7:55 a.m.

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AGENDA

Thursday, 12 December, 1996

0755	Opening Remarks	Dr. Fletcher
	Introduction of New Members/ Consultants	COL Fogelman
0815	Operation Joint Endeavor Update	MAJ Ludwig
8045	Operation Joint Environmental Surveillance Program	Mr. Resta
0915	Malaria in U.S. Forces Stationed in Korea	LTC Craig
0945	BREAK	
	QUESTIONS FOR THE BOARD	

1000	Is it necessary to conduct G-6-PD Screening Prior to Primaquine Therapy?	MAJ Ockenhouse
1050	Pre-deployment Hospitalization Patterns for Individuals on the VA Gulf War Registry	Mr. Writer
1120	Post-War Hospitalization Experience of Persian Gulf Veterans	CAPT Gray

AGENDA (Continued)

1200	WORKING LUNCH AND AFEB PHOTO	
	AFEB Activity Reports	
	- Effects of Low Level Exposure to Chemical Agents	Dr. Perrotta
	- BW Vaccine Recommendations	Dr. Allen
	- Air Force Safety Center Visit	COL Jones
		Prof. Baker
	- ARD Surveillance Meeting	Dr. Gwaltney
1300	An Overview of DOD Accession Medical Standards Analysis	

	and Research	LTC Kelley
1330	Active-Duty National Mortality	Dr. Helmkamp
	Profile (1980-1993)	LCDR Kennedy
1345	USUHS Data Analysis Center	CAPT Cunnion
1400	BREAK	
	QUESTION FOR THE BOARD	
1415	Can HAVRIX and VAQTA Hepatitis A	
	Vaccine be used Interchangeably?	LTC DeFraites
1500	EXECUTIVE SESSION	
	- Recommendation for Routine	Dr. Fletcher
	Clinical Services	Dr. LaRosa
	- Review of AFEB Priority List	
	- Committee Breakouts	
1700	ADJOURN	

P R O C E E D I N G S

(Time Noted: 0920)

THIS BOARD MEETING WAS JOINED IN PROGRESS.

SPEAKER No. 3.

LTC CRAIG: Good morning.

I'd like to present to you the actions of the EPICON team in malaria concerning a reemergence -- excuse me -- in Korea concerning a reemergence of malaria in U.S. troops.

If you'd turn the lights on just a minute, please. Lights, please?

(Pause.)

(Slide shown.)

LTC CRAIG: Thank you. North Korea, South Korea, demilitarized zone. This is the Imjin River. Seoul, Moonson and our area of concern was roughly here (indicating).

Taesong Dong Village is about here in the DMZ Pan Mujong is here (indicating), Route 1 comes south, connecting Moonson and on into Seoul. So our area is right here and I show that to you because I have a slide and I'm not sure that it's really going to present as well as I'd like.

AUDIENCE PARTICIPANT: How big is it?

LTC CRAIG: The lights can go down now, thanks.

The members of our team were Major Promotable Chris Ockenhouse, Malariologist; Dr. Ed Evans, Entomologist; Major Lis Keep, who is chief of preventative medicine at Fort Drum was physician epidemiologist with our team; Captain Promotable Bill Hewittson was the assistant team leader; and Captain Connie Bell was a parasitologist. And all of them did an outstanding job and I hope that I can present their work well this morning.

(Slide shown.)

LTC CRAIG: This slide that -- this slide that I mentioned is here. Again, the demilitarized zone is here, the Imjin River is here, Pan Mujong here, Taesong Dong Village here, and the cases in U.S. troops all occurred north of the Imjin in this region and that's why I wanted to show that to you.

The situation as of about 1 September or first week of September was that 10 cases of plasmodium vivax malaria had been detected in U.S. troops north of Imjin River.

The 18th MEDCOM had implemented anti-malarial measures to include chemoprophylaxis. This

started in August.

The 18th MEDCOM requested an EPICON team to investigate and provide recommendations for a long-term malaria control strategy.

(Slide shown.)

LTC CRAIG: Historically P.vivax has a long -- has been a long-time problem in Korea.

There was a Korean strain with a long incubation troops. It was found in Japanese troops and observed and described by Hasegawa in 1913.

This long incubation period extended out to about eight or nine months.

Malaria in Korea has been focal historically with little areas of high intimicity both in the mountains as well as the rice paddy regions. And in other areas where malaria is very rare.

During the 1930's and '40s a lot of research and study of malaria went on in Korea. And it was showing a declining trend until the Korean War. It again became a significant public health problem and the U.S. suffered about 3,000 cases.

After the war the declining trend continued until the Republic of Korea was declared malaria

free in 1979.

(Slide shown.)

LTC CRAIG: The current epidemic looks like this graphically. The dark blue are ROK army soldiers, the civilians are in the darker blue, and U.S. cases are in the red.

In 1993 the first ROK soldier was found to have P.vivax, in '94 they went up to 17, 88 in '95, and 157 by the end of September. And I might mention that from the end of September to the end of October the ROK army had 300 plus cases.

And in the U.S. population we had zero, in '94 there was one soldier with malaria, in '95 there were none, and this year we have seen -- as of 30 September we saw 10 cases. There have been two more since that time.

(Slide shown.)

LTC CRAIG: All U.S. cases occurred north of the Imjin River, five in the joint security area, and in this area soldiers live and train. And they had a rate of 1.2 cases per thousand soldiers per month for the six-month malaria season. There were five cases at Warrior Base. I could not determine incidence rates there because this is a -- has a

very transient population of troops coming in and out during the year for training, and we were just not able to get the appropriate denominator. We are continuing to try to do that now.

Two additional cases have been found. All of these cases were enlisted. Nine cases were U.S. nationals and three were in Katusa or Korea augmentee to the U.S. Army troops. The average age was 27 years. The average time from symptom onset to diagnosis was seven days. All were blood smear positive for P.vivax and all responded to standard treatment.

(Slide shown.)

LTC CRAIG: Anopheles senensis has been the predominant species coming to human bait. And we suppose that this is the vector for the recent outbreak. It's a zoophilic, rice paddy breeder, resistant to organophosphates in the lab, however, still susceptible to pyrethroids.

ELISA based ineffectivity studies conducted here at Walter Reed showed a .28 percent mosquito infectivity at Taesong Dong Village and a .026 percent infectivity rate at other sites along the demilitarized zone.

(Slide shown.)

LTC CRAIG: The parasite is P.vivax. It demonstrates both the short as well as the long incubation periods. So far it's been sensitive to Chloroquine and Primaquine treatment.

(Slide shown.)

LTC CRAIG: Our conclusions were that P.vivax has re-emerged in Korea over the past three years. That the number of clinical cases have increased dramatically in each of these years.

A. sinensis does appear to be the vector.

Currently P.vivax is sensitive to Chroloquine and Primaquine.

The mosquito infectivity rate is low.

The transmission rate in U.S. forces is low as well.

And the U.S. epidemic is focal in nature, in that all forces are north of the Imjin River and all of these forces must be considered at risk.

(Slide shown.)

LTC CRAIG: Our recommendations.

(Slide shown.)

LTC CRAIG: Number one, the objective is to minimize the occurrence of malaria in U.S. soldiers

living and training north of the Imjin during the 1997 malaria season and thereby prevent malaria from significantly impacting military and medical operations.

(Slide shown.)

LTC CRAIG: These recommendations are based on the following assumptions:

(1) That the soldiers will strictly comply with the personal protective measures;

At vector control measures will be appropriately implemented;

Health care providers will maintain a high index of suspicion for the disease;

And that intensive malaria surveillance will continue year round.

(Slide shown.)

LTC CRAIG: As far as -- excuse me -- as far as vector control recommendations we recommended that larvacides and adulticides be used to treat all living areas; the buildings and the tents in the JSA as well as in the warrior based-area should be sprayed with residual pesticides; vector surveillance should be continued; and pesticide resistance testing should also be continued.

(Slide shown.)

LTC CRAIG: For personal protective measure, we would like to see the re-emphasize that these protective measures work when used and used appropriately.

Ensure that all buildings are properly screened in the areas mentioned.

And increase the soldier education and awareness about the malaria threat.

(Slide shown.)

LTC CRAIG: As far as the diagnosis of malaria goes we've recommended that anyone with a 100.5 fever or history of fever and chills with or without the headache, malaise, back pain, and myalgias should be observed for 48 hours.

Thick and thin smears every 12 hours times four and with each fever spike should be performed. These blood smears should be taken to the 121 General Hospital without delay and once there they should be processed within 12 hours.

Post-diagnostic smears should also be performed to confirm the cure.

And patient education concerning relapses, and then for those who have had the disease as well

as for those who are found to be smear negative should be increased.

(Slide shown.)

LTC CRAIG: As far as Chemoprophylaxis goes do not recommend chemoprophylaxis for the 1997 season, however we do recommend that a contingency plan be established for implementing chemoprophylaxis in troops north of the Imjin River and that's whether they're training or living there.

(Slide shown.)

LTC CRAIG: This prophylaxis plan should be based on a number of considerations: (1) whether a threshold number of cases have occurred, and that's something that the local commanders are going to have to determine on their own. They should -- one of our
-- our guidelines of that would be whether it's impacting military operations, would be on way to look at it. And then you start chemoprophylaxis from whatever number you think that is.

The cost of chemoprophylaxis for prophylaxing the JSA, that will cost about $40,000 per year. That's for 700 folks that are at the JSA.

The warrior-based population that I mentioned as very transient I think had -- would be a much greater number of folks moving in and out of that area.

We have to remember that adverse reactions do occur. Excuse me. In using Chloroquine as well as Primaquine if the chemoprophylaxis is used, must remember that it will not prevent malaria 100 percent because you can't really control very well how people will take their chemoprophylaxis and there is always is the risk of drug resistance both through Chloroquine and Primaquine when you implement a mass chemoprophylaxis program particularly over a number of years.

(Slide shown.)

LTC CRAIG: And our last recommendation would be that these recommendations be reevaluated annually for any changes that might be needed.

That's all I have. I'll entertain questions.

COL FOGELMAN: Can we have the lights, please.

DR. FLETCHER: Thank you, sir. An

questions or comments? Dr. Chin?

DR. CHIN: Jim Chin, I was struck by your figure that showed the rate or the numbers of cases in ROK, civilian, and U.S. Do you have any explanation for the relatively small numbers in civilians? Is it just a matter of denominator or what?

LTC CRAIG: That could -- could be. What the physicians in the ROK army have found that most of the civilian cases were ROK soldiers the year before. All right. So, it appears that the reservoir for this is
-- well, it appears that it may be the ROK army that is continuing this from year to year.

DR. CHIN: You don't think that there's a significant problem in the civilian community in that area?

LTC CRAIG: It doesn't appear so right now, sir.

DR. FLETCHER: Dr. Schaffner?

DR. SCHAFFNER: The cases in the Republic of Korea's troops, are they also in the same geographic area?

LTC CRAIG: They are scattered along the

whole 110 kilometer area of the demilitarized zone.

DR. SCHAFFNER: And --

LTC CRAIG: And the U.S. troops don't normally train with them on a routine basis.

DR. SCHAFFNER: What's the flight range of anopheles sinensis?

LTC CRAIG: I don't know the answer to that. I don't think there have been any flight studies done on that particular species. But, my entomologist said it was what, about one and a half to two kilometers if it was similar to other anopheles species.

DR. SCHAFFNER: Well, if the -- I guess I'm kind of feeling my way along here. If the reservoirs is punitively in the Republic of Korea's soldiers, then the link is the mosquito and what do we know about mosquito abatement activities being undertaken by the Republic of Korea among their own troops and along that whole area?

LTC CRAIG: They're not a great -- there's not a large vector control program at this time as I understand from talking with the Korean authorities at the National Institutes of Health in Seoul.

LTC DeFRAITES: Yes, this Bob DeFraites.

COL FOGELMAN: Speak up.

LTC CRAIG: Right. Go ahead, Bob.

LTC DeFRAITES: Well, the question is, do you know where the reservoir is? Do you think this is being introduced each summer, or is there a local reservoir that over winters for Korea, or what's the story? What's your best guess?

LTC CRAIG: My best --

LTC DeFRAITES: My second question is, what are the Koreans going to use prophylaxis in their troops along the DMZ?

LTC CRAIG: Yes, the Koreans are going to use chemoprophylaxis next year or so I've been told by Bill Novokofsky.

And restate that first question real quick?

LTC DeFRAITES: Well, where do you think the malaria is being introduced?

LTC CRAIG: Originally when we hit country thought that it would probably be a reservoir found in the Taesong Dong Village which is the propaganda or demonstration village on the DMZ. But as you saw the mosquito infectivity rate there is very low. In fact, it's low all along the DMZ. So I'm not real sure where the inciting mosquito came from or where

the reservoir originally was. But it certainly appears that the Korean army is now the reservoir or the significant reservoir and country for where you see this transferred from year to year.

I think and I don't have any data on this, it's just a personal opinion from talking with Korean physicians there, but I think their -- the time from symptom onset to diagnosis in the Korean troops is much longer than what it is in our soldiers.

If you remember our soldiers averaged about seven days. One of those troops was out at 24 days. So he was a -- you know, an outlier there. So it may be even a shorter period than that. But I think from talking with Korean physicians that their soldiers will go much longer before they are seen and treated for this disease. Therefore, I think they're spreading it amongst themselves quite efficiently. And then it only takes -- well, I don't know how many it would take, I shouldn't say that -- but -- but it would take a few soldiers just to have a long incubating vivax to carry that on into the next year. And that's what I think you see going on here.

DR. FLETCHER: Gwaltney I believe was next.

DR. GWALTNEY: Is the malaria on the North Korean side of the DMZ?

LTC CRAIG: I don't know that. I don't know the answer to that.

DR. GWALTNEY: Is the malaria in North Korea indemically?

LTC CRAIG: Yes, I think it has been.

DR. FLETCHER: Dr. Stevens?

DR. STEVENS: That was the same question I had.

DR. FLETCHER: Same question. Well, Dr. Walter?

DR. WALTER: Yes, could you tell us a little about your treatment protocol? I'm not sure I understand. Are you saying that anyone with -- what does it mean to be under observation for 48 hours?

LTC CRAIG: I'm sorry, they would be in the hospital on a hospital ward under observation.

DR. WALTER: Anyone with a history of fever?

LTC CRAIG: That's correct.

DR. WALTER: Whatever fever -- presumably

that wouldn't be measurable it would be hospitalized?

LTC CRAIG: That's correct.

DR. WALTER: And is treatment begun only on the basis of a positive smear or is begun --

DR. FLETCHER: Louder, Ron. Louder.

PARTICIPANT: Could you speak up, please?

DR. WALTER: Sorry. Do you begin treatment only on the basis of a positive smear?

LTC CRAIG: That's correct.

DR. FLETCHER: Other questions? Comments? Yes?

DR. STEVENS: There's a village just south of the Injim River on Route 1, I believe Mooson?

LTC CRAIG: That's correct.

DR. STEVENS: Were you able to ascertain if there are any cases there? The reason I ask this is north of the Imjin on the DMZ there's very few rice paddies. Most of the rice paddies are on the southern side of the river. And if I remember correctly the historical -- the last place they had malaria in Korea is was in the northeast part of the DMZ which is further -- quite a distance from where the U.S. sector is.

LTC CRAIG: That's correct. Each year the cases have started in the Korean soldiers in the northeast area; that's correct. But there were no cases in Moonson. There were cases in that county, if you will, but no cases in Moonson.

DR. FLETCHER: Yes.

COL KORWAKI: Steve, it didn't come out clearly in your presentation -- I'm Colonel Korwaki from MEDCOM, by the way -- two of the cases, as I recall, were actually diagnosed in the United States. One in Nebraska and one in Georgia, I believe.

LTC CRAIG: That's correct.

COL KORWAKI: Just from a public health perspective, obviously these soldiers had left Korea. Their incubation periods were long enough that they actually came back to the United States and became symptomatic at that point. One, I believe, was even in a VA hospital not in one of our military treatment -- medical treatment facilities. So from a public health perspective we're under -- you know, we have the perspective possibility of introducing cases back into the U.S. that folks need to be aware of.

And, again, your index of suspicion needs to extend far into the civilian community as well, or at least the soldiers need to be made aware that they were potentially exposed. They still run a risk of becoming ill when they're back in the United States and in need of treatment at that point.

LTC CRAIG: Correct. And we did mention in our recommendations that soldier education, both coming in and leaving the country was very important just for that reason.

DR. FLETCHER: If there are no other comments, we'll take a break in time to be back at 10:00. Thank you very much.

(Applause.)

COL FOGELMAN: If I could have the attention of everyone. Please, if you would, at 3:00 today or there abouts we're going to be having an executive session. We're going to be talking about the priority list that was developed by you at the offsite and then sort of pared down by the preventive medicine officers of the services. If you would review before three the handout that I gave you that I think the top sheet is Top AFEB Priorities Recommended by Service Preventive

Medicine Officers. Would you please -- yes, you should have that. If you don't, see Ms. Ward and she should be able to give you a copy.

Please review that and also take a look at the Executive Summary that I wrote for the offsite and give me any feedback on that.

DR. FLETCHER: Let me make a couple of announcements. I'd like to acknowledge Dr. Mary Lou Clements from the Department of International Health and Division of Vaccines at Hopkins. So welcome to our Board.

Are there any other Board members I've missed? I think I -- one other thing, let me acknowledge others and welcome others in the room. We have a 150-or-so mailing list for this meeting. There are 15 to 20 Board members, we have flag officers, we have the preventive medicine officers and many others who make up the total of 150. For instance, there are others like Dr. Brundage, and Dr. Bancroft who has spoken to this group before, so many people make up this meeting. So I'd like to welcome everyone in the outside circle as well as the inner circles. So thank you for being here and your input.

COL FOGELMAN: Okay. Thank you.

Our next speaker is going to be Major Chris Ockenhouse who is an infectious disease physician and malariologist with the Department of Immunology at the Walter Reed Army Institute of Research. And this will be a question for the Board and the question will be, is it necessary to conduct G6PD screening prior to Primaquine therapy which would include prophylaxis as well. So, Dr. Ockenhouse?

MAJ OCKENHOUSE: Thank you very much. Can you hear me?

COL FOGELMAN: I think you need to use the hand-held mic. There you go.

MAJ OCKENHOUSE: I have a fairly significant case of laryngitis due to the flu. As a matter of fact, I didn't take my flu shot this year and I'm regretting it right around now.

(Laughter.)

MAJ OCKENHOUSE: I know, for infectious disease, it's pretty sad.

(Laughter.)

MAJ OCKENHOUSE: What I'd like to talk to you in the next half hour maybe 40 minutes is to look at the issue of G6PD testing. And I'll

approach it right from the beginning talking what it is, the historical aspect of it, why it matters and why the Army doesn't do it and perhaps why the Navy does.

Now, when I was first asked to consider this question, I called up one of my colleagues on the Navy and says, you know, why does Navy test its sailors for G6PD deficiency? And because we always have is -- is -- you know, is an answer that I've heard fairly often.

But what I'd like to do is actually find out what are the cogent reasons why it either should or should not be done for U.S. military personnel.

If I could have the first slide?

(Slide shown.)

MAJ OCKENHOUSE: G6PD is an enzyme, glucose six phosphate dehydrogenate. In individuals who are deficient in this enzyme it occurs as an X-linked hereditary deficiency with variable penetrance.

There are greater than 400 variants of this deficiency, mostly point mutations, insertions, and deletions. And it occurs that if an individual is deficient it may be it's not an absolute deficiency, it's a quantitative deficiency as well.

This enzyme deficiency is very interesting. It exists as a balanced polymorphism in human populations. By that I mean, it has the slight negative effects conferred on human survival is balanced by benefits conferred by the enzyme deficiency.

Now, the great paradox is why this enzyme deficiency occurs is probably because it offers protection against plasmodium falsyprum malaria.

But what we're going to deal with this morning is the problem that occurs from using drugs that we use to treat plasmodium vivax. And why the problem of G6PD deficiency and its testing is -- concerns us.

Next slide, please?

(Slide shown.)

MAJ OCKENHOUSE: The enzyme functions to reduce NADP to NADPH. This provides a source of reducing power to maintain sulfhydro groups and aids in the detoxification of free radicals and peroxides.

When this enzyme is deficient red cells specifically are susceptible to oxidative damage. The most frequent clinical manifestation of G6PD

deficiency is hemolytical anemia.

The hemolytic anemia rarely occurs spontaneously but is precipitated by a variety of insults.

Next slide.

(Slide shown.)

MAJ OCKENHOUSE: These insults -- the major category is drugs, medications. And each different type of medication can induce a hemolytic crisis in and of its own and not one hemolytic crisis induced by one drug is necessarily more severe than that induced by a different drug.

Primaquine is the protypic drug which induces hemolytic crisis in those individuals who are deficient in this enzyme G6PD. And that's why we're addressing this question because Primaquine is the mainstay in the treatment and prophylaxis plasmodium vivax malaria.

Now, there's other things that can precipitate hemolytic crisis in individuals who are deficient. And I'll just basically mention those, metabolic disturbance, diabetic ketoacidosis as well as infection. Bacterial pneumonia has been shown in several studies.

Next slide, please?

(Slide shown.)

MAJ OCKENHOUSE: To understand the significance of what we're dealing with is to understand the problems of plasmodium vivax malaria. And -- now, as a malariologist and with training in parasitology we always show life cycles. And it's very important to understand for our members here who aren't really acquainted with it, why this is an issue for our soldiers and sailors.

When a mosquito infected -- anopheles mosquito infected with malaria sporosolites which is the infected form bites you, the sporosolites go immediately to the liver. Now, when you think of malaria, you think of a blood stage infection, and that's true. That's what the clinical symptoms come from. But the initial three to five days of development of the parasite occurs in the liver. And the parasite actually invades the hepatocyte, develops and then reemerges from the liver cells to invade red blood cells.

Now, what is specific about plasmodium vivax versus other types of human malariae is that this phase can be latent in plasmodium vivax. That

means not -- after five days not all of these parasites come out into the peripheral circulation. So what we've seen in Korea is soldiers who come back after ten months, or, you know, they've been in the United States 10 months and all of a sudden come down with malaria. And that's because of these hypnozolite -- that's the name of the stage -- these latent forms that have been hiding out for 10 months in the liver.

Now, for those soldiers who have been exposed to malaria we can -- we can certainly cure the blood cell stage. And if we clear -- if we treat clinical malaria, we can cure the infection. The problem -- one of the goals in treatment is to make sure that these individuals are no longer susceptible to -- not reinfection, but to latent re-emergence of parasites into the blood from the latent liver forms. And it's this stage of the parasite that Primaquine acts at. Primaquine is absolutely essential to eradicate the tissue forms of the malaria parasite plasmodium vivax.

Now, this is not a problem with plasmodium falcipirum because it doesn't have this latent stage.

Could I have the next slide?

(Slide shown.)

MAJ OCKENHOUSE: Now, you know, malaria has been a problem in U.S. Army, U.S. Navy since the 1700s. You know, I just read the other day when I was preparing for this, that the Continental Congress Army ordered tons of Peruvian bark back in the 1700s for its troops. Because Peruvian bark that's shown on the quinine. You know, and so -- and we've had problems in World War II and Korea War and Vietnam. And this is a posters to try to tell soldiers in World War II, you have to practice protective measures. And that's the first line of defense against this disease. You try not to rely necessarily on chemoprophylaxis.

Next slide.

(Slide shown.)

MAJ OCKENHOUSE: And this is another one, you know. And, you know, it probably didn't -- in putting these posters up doesn't change people's behavior. They've had a couple hundred thousand cases of malaria during World War II.

Next slide.

(Slide shown.)

MAJ OCKENHOUSE: Malaria control, in my opinion, is -- is the responsibility of the commander. And I came across a very apropos quote that I consider from General Sir Neal Cantly who is the Director General of the British Medical Services during World War II. And they were having tremendous problems in Burma and India with malaria and people weren't taking it seriously. And he said when the -- when for the first time in history a combatant officer was considered unfit to command a unit on the grounds that he allowed his men to become ineffective through disease a new day in military medicine dawned.

And since personal protective measures cannot always work, we have to rely on chemoprophylaxis.

Next slide.

(Slide shown.)

MAJ OCKENHOUSE: And this is -- oh, patch -- I just want to make this point, patch that net hole today. You know, we give -- and these are practical problems. You know, over in Korea our soldiers aren't even deployed with nets. And so we're dealing with, you know, issues that, you know,

if we want to prevent malaria may actually have to rely on chemoprophylaxis and the use of Primaquine.

Next slide.

(Slide shown.)

MAJ OCKENHOUSE: Okay. Now, this is the historical -- Primaquine has a -- actually very interesting history. 1926 in Germany Muhlens described the use of pamaquine which is a -- which is the precursor of Primaquine which we use today in the treatment of acquired malaria. That very same year Cordes described four cases of hemolytic anemia associated with pamaquine.

Interestingly enough he said all four of these cases occurred in dark-skinned individuals. And we'll come to that in a few minutes.

Between 1930 and 1940 so many reports of hemolytic anemia associated with pamaquine were reported in the literature. Now, due to requirements of anti-malaria therapy during World War II extensive research was directed toward the mechanism of pamaquine induced hemolysis.

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MAJ OCKENHOUSE: Feldman in 1947, Earl

1948, noted an association between pamaquine use hemolysis and race. Quote: "Pamaquine acts as a precipitating factor capable of producing hemolysis when certain predisposing factors are present." You know, they found that, you know, it occurred at a much higher frequency among black soldiers.

The great difference in the susceptibility of caucasians and black populations to pamaquine induced hemolysis was noted in the 1940s. 1952 Primaquine induced hemolysis occurs in the same persons susceptible to pamaquine induced hemolysis.

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(Slide shown.)

MAJ OCKENHOUSE: Now, the incidence of G6PD deficiency is related to the -- the penetrance of -- it's actually manifested in certain populations. Kurdish Jews have -- the males have a 62 percent incidence of being deficient in this enzyme. The deficiency is actually fairly severe. Less than 5 percent residual enzyme activity.

Whereas in black Americans, black males, about 8 to 10 percent of all black American males are deficient in the enzyme. This is not a severe deficiency. They usually have 10 percent or greater

enzyme -- residual enzyme activity.

In Sardinia we've -- cases of 30 percent and caucasians less than .1 percent.

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(Slide shown.)

MAJ OCKENHOUSE: Now, the linkage of Primaquine induce hemolytic anemia and the intrinsic abnormality of the red cell, this is the important point, very interesting work actually done by the United States Army Malaria Research Unit working out of the University of Chicago and at Stateville Penitentiary. Actually it's some very elegant classic studies on experimental malaria in humans were done back on the 50s at Stateville Penitentiary.

Dern and colleagues including Alvane found that it was the Primaquine induced hemolytic anemia was related to a specific enzyme deficiency. And it was that biochemical basis showing that hemolytic anemia due to Primaquine was due to individuals who are deficient in G6PD.

Could I have the slide off a second.

(Slide shown.)

MAJ OCKENHOUSE: Now, this is -- I hope you

can see this. This is the reason why it is important to give Primaquine for malaria for vivax malaria. And this is vivax in Korea. During Korea there were 30,000 cases of vivax malaria. Now we -- I just got back from Korea the 10th. So we have to keep it in perspective here.

We had 30,000 cases. When individuals were only given Chloroquine you had an enormous amount of relapses. That means you can clear their total infection, but several weeks later because of this tissue phase they will relapse. If they were either given pamaquine which we no longer use, or use Primaquine, 15 milligrams -- this is the standard dose that we used in the United States and worldwide today -- daily for 14 days, we find that the percentage of relapse is zero.

Now, this will vary according to the type of plasmodium vivax strain that exists. Now, in Korea it's extremely sensitive to Primaquine, so it is absolutely essential that our soldiers -- for treatment receive Primaquine.

(Slide shown.)

MAJ OCKENHOUSE: Now, I'd like to show you some data about this association between race and

individuals with G6PD deficiency and Primaquine-induced hemolysis. Now, this is a laboratory experiment, very elegant, and actually people still do it today. Not in the United States, but in other countries. What they do -- let me just explain -- if you take red cells from an individual who is sensitive -- who is G6PD deficient, their red cells are susceptible to lysis -- and you label them with radio-active chromium and then you infuse them or you transfuse those red blood cells into individuals -- normal individuals without enzyme deficiency who are taking Primaquine, you can see that those labeled red cells from an individual who is deficient in G6PD are lysis. This is the percent of -- or a fraction of chromium labeled cells remaining the circulation. If an individual doesn't receive Primaquine they don't get lyses. So we know that there's a scientific basis for Primaquine-induced hemolytic anemia.

(Slide shown.)

MAJ OCKENHOUSE: Likewise, if you do the opposite. If you take red cells from an individual who is not deficient -- most of us in this room -- and you label them and you put them into individuals

who are G6PD deficient, they don't -- you don't get lysis of the red cells. However, in individuals who is G6PD deficient and is placed on Primaquine for a period of -- here six days -- will drop their hematocrit.

The point of this is to actually -- people actually showed that the absolute linkage between a drug and enzyme deficiency and hemolytic anemia.

Slide back on.

Next slide, please.

(Slide shown.)

MAJ OCKENHOUSE: A certain amount of facts I'd like to show to you. American blacks with G6PD deficiency their erythrocytes are less susceptible to hemolysis. The amount of enzyme is diminished but not absent. Caucasians with G6PD deficiency especially those like from Sardinia their erythrocytes are much more susceptible to hemolytic effective therapeutic doses of drugs.

Kellermyer and Jama 1962. By the way, most of the literature I'm reporting is literature probably 30, 35 years old. It is still, in my opinion, the best literature.

The hemolysis induced by giving dose of

Primaquine in negro males who are otherwise healthy is both predictable and reproducible. The course of hemolysis induced by Primaquine serves as a basis for grading the relative hemolytic effect of other therapeutic drugs.

So Primaquine is the prototypic drug when one studies G6PD deficiency and hemolytic anemia. But we should only be concerned about its use in Primaquine and U.S. soldiers.

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(Slide shown.)

MAJ OCKENHOUSE: Now, there's a direct correlation between the amount of residual enzyme activity and the severity of hemolysis. Approximately 10 percent residual enzyme activity is associated with a mild self-limited anemia. I'd like to stress that point.

All American blacks with G6PD deficiency possess residual enzyme activity. Hemolysis is directly related to the dose of the offending drug. I'd like to show you some data for that.

Light off, please.

(Slide shown.)

MAJ OCKENHOUSE: Now, I'd like to show you

this first graph because there's a lot of really very important information and it's presented in a way -- 1960 bulletin of the World Health Organization. If you give -- if you put a person on 30 milligrams of Primaquine daily, that's twice what we use now. However, it is a dose which is sometimes necessary if individuals fail therapy at 15 milligrams a day. But if you give Primaquine 30 milligrams daily to an individual who is G6PD deficient, you see a fall in the hematic rate. You go through acute hemolytic phase. This is always self-limited.

The hematocrit drops and then the bone marrow recovers with a reticulocytosis. So you see the reticulocyte count goes up and you get recovery of the hematocrit even in the presence of 30 milligrams of Primaquine.

And what this is due to is that the drug is actually destroying the older red cell population. It's the young red cells which are fairly resistant to the hemolytic effect. So if you're destroying the old red cells, you're going to get a hemolytic anemia and then you're going to get recovery.

(Slide shown.)

MAJ OCKENHOUSE: Now, as far as dose response, it was thought because of a -- they wanted to, back in the Korean war, looking at our soldiers with -- who had vivax malaria what would be the best dose to give? Now what we -- if you give -- this is the same individual. This is an individual where if you give a course of Primaquine -- this individual is G6PD deficient, by the way. So if you give a 30 milligram dose you get a precipitous decline in the hematic rate, down to about 30. That's much higher than one wants to see, of course, and -- what they then showed that if you allow a washout period, challenge this individual, oh, six months later, they did this on an every six-month basis with a lesser amount -- 15 milligrams -- you get a much less hemolytic effect.

And this is -- this is 14 daily doses. Now, why do we do 14 daily doses? Well, there's a lot of practical reasons why we give the drug for only 14 days and number one is compliance. You want to make sure that your soldier or your sailor is going to get the medicine and is not going to have a relapse of malaria. And so it was -- it was -- and I'll show you some data about why the 15 milligrams

of Primaquine was advocated and not the 30 milligram.

But very interestingly enough if you give 45 milligrams -- that's three times the does, but you only give it once a week, but you give it for eight weeks, you get absolutely no hemolysis. You do get a little bit with 60 milligrams. And this is an extremely effective prophylaxis regimen for individuals who have been exposed to plasmodium vivax.

The problem with this as was seen in Korea and Vietnam is compliance, the greater relapse rate because you have to rely on a soldier while they are well, they are not ill, to take a medicine once a week for eight weeks. And they probably are not going to do it.

Slide please.

(Slide shown.)

MAJ OCKENHOUSE: The anemia from hemolysis is predicable, stable and self-limited. I just went through some of that data. There is no evidence of hemolysis till two to three days after the first dose. Subsequent administration of the Primaquine does not shorten the latent period. So you can keep

-- actually you can keep on giving the drug. Although, if we ever had a soldier who came in with hemoglobin urea or, you know, itecsclera, of course, we would stop the medicine.

Severe hemolytic anemia it can occur, you know, and this is usually chronic. All right. This is in individuals who are of Mediterranean decent with severe enzyme deficiency -- Sardinia. And its symptoms include weakness, abdominal pain, back pain, decrease in hematocrit reticulocytosis. You see that also with mild anemia.

Next slide.

(Slide shown.)

MAJ OCKENHOUSE: What is the military experience? This is important. Primaquine was first used on a large scale during the Korean conflict. A single does was administered to greater than 250,000 troops. Approximately 10 percent back then were black. During 10 to 14 day trans-Pacific voyage. Hey, this is when they were ships and it's easy to give a drug like Primaquine once a day on their way back to the United States for Korea. And this was the therapy that was instituted. There was no testing for G6PD deficiency.

It's been reported, although I -- you know, -- it's -- it's hard finding numbers on the amount of hemolytic reactions. I can't believe that there is only a half a dozen. But according to the -- you know, the literature, I can only report what I can find, is that there was only about a half dozen hemolytic reactions were reported. That's probably an under estimate as we'll see from Vietnam data.

The relapse rate from vivax was only 1 percent, so this is significantly better than individuals who don't get Primaquine for their vivax malaria.

Next slide, please.

(Slide shown.)

MAJ OCKENHOUSE: Now, on the basis of additional clinical trials, Alving predicted -- he first predicted -- which is very interesting -- and then he demonstrated it. That a single 45 milligram tablet a week for eight weeks is -- has effectively prevented relapse.

I think it probably needs a little bit of focusing.

Hemolytic anemia was not demonstrated with this dose of Primaquine in males with G6PD

deficiency. This is an important point. We know that giving a drug of 15 milligrams or 30 milligrams of Primaquine a day will induce a hemolytic anemia; 15 milligrams a day can induce a mild case of hemolytic anemia, but 45 milligrams once a week does not.

Now, this regimen was considered superior to the 14-day Primaquine course and was the preferred drug for malaria chemoprophylaxis. And this is the source.

Next slide.

(Slide shown.)

MAJ OCKENHOUSE: Now, in Vietnam -- this is the only quote I could come up with looking through the literature. There was a small but continuous evacuation of G6PD deficient troops from Vietnam because of hemolysis secondary to Primaquine sensitivity averaging 17 per month. Most of these patients were black. And anemia took a mild form in this ethnic group. Despite a recommendation to challenge troops with a single CP this was combined Chloroquine, Primaquine tablet prior to departure to Vietnam from the United States, no official screening policy was adopted.

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(Slide shown.)

MAJ OCKENHOUSE: Now, discussions concerning -- now, you know, in Vietnam there was just not plasmodium vivax there was a significant problem with plasmodium falciparum. And for the very first time we started receiving reports of drug resistant Chroloquine resistant plasmodium falciparum. So multiple drug regimens had to be instituted. And that included pyrimethamine, quinine, it included dapsone. And there seems to be -- there's a misconception that a lot of individuals who -- a lot of our soldiers who came down with a granulocytosis during Vietnam, you know, acute hemolytic anemia was due to Primaquine. That's in fact not the case. It was really due to a combination of offending agents. The major one was dapsone or sulfa.

Now, it was believed that the weekly CP tablet should be -- the routine method of chemoprophylaxis and should also be given following therapy for clinical malaria in preference to the 14-day Primaquine regimen. The potential problem with G6PD deficiency was recognized, but the

efficacy of Primaquine in eradicating the tissue phase was considered overriding.

Could I have the slide off just for a second? I want to show one additional piece of data.

(Slide shown.)

MAJ OCKENHOUSE: I want to show you some data here which I think is important to understand why the 45 milligram versus a weekly dose is efficacious.

Individuals who just got chloroquine for their plasmodium vivax you would expect to have relapse because it doesn't affect -- the chloroquine affects the blood stage but not the tissue liver stage. And you had an increased amount of failure in individuals who had vivax who just chloroquine. So this serves as your control group.

Now, if you look here -- look down here. This is what we do now a days, 15 milligrams of Primaquine daily for 14 days. You can even -- with giving that regimen, you have a relapse rate of about 27 percent. Now, this is what we typically do in the United States. It's what the CDC recommends. However, of you look at a -- if you give 45

milligrams of Primaquine -- and the reason I bring this up again is because it doesn't cause any hemolytic anemia. Once a week for eight weeks you're -- the amount of therapeutic failures relapse rate is about 10 percent.

So, you know, it is almost three times less than receiving Primaquine on a daily basis for 14 days. So this suggests that -- you can quite give safely Primaquine daily, you know, and those individuals who are enzyme deficient may indeed come down with hemolytic anemia.

However, there's alternative ways of looking at it. You can give Primaquine anti-malariae weekly. The problem with this is are your soldiers going to be compliant.

May I have the slide on please? And the next slide.

(Slide shown.)

MAJ OCKENHOUSE: Now, what are the factors -- excuse me -- what are the factors to consider when formulating recommendations on whether to test for G6PD deficiency? This is my last slide.

Now, these are some of the factors that I came up with. I'm sure there's plenty of other

factors.

Number one, does the risk of Primaquine-induced hemolytic anemia outweigh the benefit from protection against plasmodium vivax malaria for U.S. service men and women?

Does qualitative testing -- that's what we do now in most labs in the United States -- the Navy does a qualitative test -- predict which individuals will suffer Primaquine-induced hemolytic anemia or does it only identify those at risk?

Another question, is hemolytic anemia a predictable outcome from standard does of Primaquine used in the treatment in prophylaxis and P.vivax malaria? I addressed some of those points with some of the data I just presented.

Fourth, does G6PD testing alter the practical institution of chemoprophylaxis in service people? This is an important point. If you test your soldiers for G6PD is that information available at the time when one needs to use it? You know, there's a anecdotal reports. Individuals coming back from Somalia and getting off the plane and giving their Primaquine tablets as soon as they're getting off the plane. You know, medical records

are sometimes with them, sometimes not.

And the fifth issue is, you know, is testing cost effective? Something to obviously include in the equation.

Well, thank you very much. I'd be willing to entertain any questions.

DR. FLETCHER: Thank you, Major.

(Applause.)

DR. FLETCHER: How about some questions? Yes, sir.

CAPT CUNNION: I'm Capt Steve Cunnion, ESUHS. I apologize for the Navy officer that didn't have the correct answer for your -- why the Navy gives G6PD testing. The reason is, is that we don't have the luxury of hospitals when we have people coming down with clinical malaria. Some of our people come down aboard ship which don't have complete laboratory facilities. And at that time it was the clinical practice to do a G6PD testing when you're treating personal malaria so when you gave them terminal prophylaxis. And because we did not have those facilities aboard ships, we decided to just G6PD test everyone beforehand so it would be in their medical records if they did get malaria and

had to be treated aboard ship.

DR. FLETCHER: Other questions, comments?

COL FOGELMAN: This is a question that the Board will be asked to respond to at some point even if not by the end of this meeting. So if you have additional questions for Dr. Ockenhouse we can ask him to come back or whatever?

DR. FLETCHER: Dr. Chin?

DR. CHIN: Two questions, one, is there reason why 45 doesn't cause any -- 45 milligrams doesn't cause hemolysis? That's question one.

And two, has this policy question ever been raised before in terms of questioning G6PD because the data you're presenting is not new.

MAJ OCKENHOUSE: You're absolutely right.

Well, to the first -- to the first point, why the 45 milligram doesn't cause any hemolysis. I don't know the answer to that. All I knew of this report is what I had seen in the literature. I suspect because you probably -- the problem is probably drug levels. You probably need a certain level in the blood in order for the red cells to be sensitive to it. And you're only given it once a week.

Now, as far as why this issue hasn't come up before, I don't know, you know. This is an issue which comes up all the time for us in the Army. Every time we deploy whether we deploy to Honduras, or Somalia, or Korea, the issue is, should we be testing our individuals -- our soldiers for G6PD deficiency? And the answer is, no, because we don't do it. Now, is that a cogent reason. It's only cogent if you can have some data to back it up.

COL FOGELMAN: Dr. Clements?

DR. CLEMENTS: Yeah, how sensitive is the test for G6PD?

MAJ OCKENHOUSE: I don't know. I mean, it's a qualitative test. I -- honestly I don't know what the sensitivity, specificity. I suspect it's fairly sensitive. Most clinical laboratories will -- will report it. It certainly won't tell you any information that's going to be -- won't tell you how deficient you are. That's a quantitative test which would really -- which will take a lot more effort and a lot more money to do quantitative testing.

DR. FLETCHER: Dr. Perrotta?

DR. PERROTTA: What will happen to a soldier, sailor, airman who tests positive for this

who is deficient -- in a deployment that's going to a malaria zone? Maybe the Navy can answer that, but what will happen to this person who is going to be deployed and all of a sudden finds out or maybe finds out earlier that he can be deployed there?

MAJ OCKENHOUSE: I don't know if that's a -- actually I'm not sure that's an exclusion. They exclude individuals who are G6PD deficient from being deployed to malaria areas.

PARTICIPANT: No, they don't. We do -- we give all our therapies or we don't give chemoprophylaxis at all. We watch those people or we continue -- for eight weeks past that. So we just -- we -- for where they are G6PD deficient we don't give them thermoprophylaxis and we follow them closer.

DR. FLETCHER: Dr. Waldman?

DR. WALDMAN: Yes, could you give us some more information about the basis for the dosage regimens that you've given? Either a weekly doses or 14 daily doses of 15 milligrams, what's the foundation for that duration of thermoprophylaxis?

COL FOGELMAN: Could you repeat the question, please?

DR. WALDMAN: Yeah, I'm asking about the basis for the duration of therapy. We've shown two regimens, one of eight weekly doses and another of 14 daily doses of a lower dose. And the suggestion from the data was that if you could reduce the duration of therapy that the rates of the hemolysis might be considerably lower.

MAJ OCKENHOUSE: Well, if I said that, I don't mean to imply --

DR. WALDMAN: No, you didn't say that.

MAJ OCKENHOUSE: Oh, okay.

DR. WALDMAN: I just saw it from --

MAJ OCKENHOUSE: Oh, from the literature.

DR. WALDMAN: From the literature.

MAJ OCKENHOUSE: You know, I looked at this. It's surprising that there's only two -- two -- this work comes out of looking at experimental vivax malaria in U.S. prisoners and also in field situations in Korea and Vietnam. I have not come across any dose ranging studies. No, I've come across dose ranging studies where they look at 7.5 milligrams, 15 milligrams, 30 milligrams a day; 7.5 milligrams a day is insufficient and it caused a much too high relapse rate. So 15 milligrams a day

while it has a higher relapse rate, it was thought to have a margin of safety built in that at 30 milligrams a day one didn't see.

Now, as far as timing, the dose duration -- you know, this is like a lot of things in infectious disease, you know, you kind of just do it for a period of time, but nobody looks at how short one can do. The only literature that I've ever seen is looking at two weeks versus once weekly.

Now, if there may be something out there looking at something else, but I really don't think so.

DR. FLETCHER: Yes?

LTC SMOKE: I'm Lieutenant Colonel Smoke from WRAIR. I have two comments. One, when this initial dosing regimens were being formulated for the military out of Korea this data was presented to the National Science Council for their approval because at that time they did know of G6PD deficiency. And the Council then recommended that it not be done for, you know, a number of reasons. And I believe that's footnoted in some of these early JAMA articles.

Secondly, about dosing, as Major Ockenhouse

has said, vivax has many different strains and actually are very -- the strains are different, are very different sensitivities to Chloroquine so that in India they have tried to go down to a seven day regimen for -- with 15 milligrams and found that it didn't work. In other countries they -- you know, they have tried to alternate. I think in the United States we kind of just settled on 14 because we don't know where our soldiers are going to be picking up their vivax infection and how sensitive that particular strain will be to chloroquine.

DR. FLETCHER: Yes?

DR. LaROSA: I have a couple of questions. First I gather this is sex-linked. It does not occur in females; is that correct?

MAJ OCKENHOUSE: No, no, well, it occurs mostly in X-linked in males, but it does occur in heterozygous females but of lesser frequency.

DR. LaROSA: Okay. Number two that the test is -- it can tell you whether or not you have the deficiency but not the extent; is that correct?

MAJ OCKENHOUSE: Correct. You can test for quantity -- you can do quantitative testing.

DR. LaROSA: Okay. And there is a range of

responses then in amongst black populations. I noticed one thing on one of your pages here that it tends to be of lesser severity, the hemolytic anemia in blacks, but there's one Air Force report of a black male who developed a severe hemolytic anemia. So there are a range of responses also amongst blacks?

MAJ OCKENHOUSE: Right. Well, you know, if you look at -- right. Okay. That's absolutely correct. There is a wide range and effect you can't predict.

Now, you can either -- the severe hemolytic anemia is usually an acute hemolysis. It occurs very rapidly and -- but it plateaus off. Now, I haven't come across any reports of any, you know, of bad out -- deaths. Actually, but, you know, that's not true. There's something that's been referred to in 1920, one of the first individuals given Primaquine working out in the Mediterranean, probably an individual with probably no residual enzyme activity, they said died, but it was just an anecdotal report that somebody died.

But you're absolutely correct. There's a wide range of hemolytic effects. And the fact is

that we don't see it very often, you know. And if you do see it, you know, you can stop medication. But usually it will run its course whether you continue the medication or you stop it.

DR. LaROSA: My last question is, what, if any, literature do you have on male/female differences and responses to treatment?

MAJ OCKENHOUSE: Oh --

DR. LaROSA: I understand it's vanishingly small in females, but --

MAJ OCKENHOUSE: Right.

DR. LaROSA: -- nevertheless.

MAJ OCKENHOUSE: In response to treatment -- you mean in Primaquine -- you mean for vivax malaria?

DR. LaROSA: Yeah.

MAJ OCKENHOUSE: Oh, I think it's probably equally effective, but I don't have any data on that. I've never seen anything that was sex differences in the ability to respond to --

DR. LaROSA: Well, but the negative response to it -- to the hemolytic anemia?

MAJ OCKENHOUSE: Oh, oh, I see what you're saying. Oh, oh, yeah.

DR. LaROSA: As a result of?

MAJ OCKENHOUSE: Most of the cases have always been reported. Most all the cases are males. Females have a much lesser hemolytic crisis -- hemolytic anemia than males, but it's been reported. Especially, you know, if you're heterozygous.

DR. FLETCHER: Microphone to the right.

LTC SHANKS: I'm Lieutenant Colonel Shanks from the U.S. Army lab in Kenya and I want to give you two cautionary tales from actual experience that may speak to some of the issues that Major Ockenhouse has brought up. One, the business about 45 milligrams of Primaquine not causing a lot of hemolysis. Although this is probably true in people with minor G6PD, but it's not in other ethnic groups. Specifically, the Thai army had an incidence of about one in a thousand of their men put on CP tablets during Vietnam having severe hemolytic reactions when deployed and I've -- we've personally taken care of a Thai soldier who would have died had he not have gotten five units of blood in two weeks of hemodialysis from what was, I think, only 30 milligrams of Primaquine for his vivax malaria treatment.

So, although it's not common in American blacks, there are other ethnic groups which are represented rarely in the American military that this can become a life threatening event. And also speaking of another allied army that I had the privilege of co-working in, in the Australian army, just because you identify the G6PD deficient people in your population does not in any way assure that you're going to manage to get around the disastrous events you're trying to do.

I remember one sergeant whom I identified as G6PD deficient wrote all over his chart in red, spent 30 minutes counseling the soldiers, spoke to his commanding officer and on his return from Papua, New Guinea he was given Primaquine by his sergeant who insisted that they all had to take it. And on a field training exercise at the end of a very long phone line turned very yellow and got very sick. I wish I could say this would not happen in the American military, however, I know better. Thank you.

DR. FLETCHER: Thank you. Other comments? Yes, sir?

MR. NUEGA: Van Nuega from the EMED Center

and School. Two questions, what is the positivity rate in the Navy on the testing the screening? And the other question is, has anybody looked at hospitalization for hemolytic anemia due to Primaquine?

MAJ OCKENHOUSE: I don't know what the incidence of G6PD deficiency in the Navy, I suspect that it's not going to be that much different than what's been reported in epidemiologic studies looking at different ethnic groups.

What was the second question?

MR. NUEGA: The hospitalization --

MAJ OCKENHOUSE: Oh, hospitalization. No, I haven't -- I don't have any information on that.

LTC SMOKE: I can address that question. We have attempted to do that, but the way the ICD9 codings are, it's almost impossible to separate that and Primaquine as a cause without going to individual records. So, as far as I know, nobody in the service has actually taken it that one step to try to verify. You can look. When you look you can find, you know, maybe 100 cases, but you can't really be sure that it's due to Primaquine because of the way the coding is done.

DR. FLETCHER: Other questions, comments? If not, Dr. Sheppard, I understand -- wait a second --

CAPT TRUMP: Captain Dave Trump with the Navy. Just to follow up. I'm not aware that we've looked at, you know, the prevalence of G6PD deficiency. We obviously do the testing. A sort of follow-up question is, and it probably merits a look is we certainly have a demographically different military with much more -- a bigger percentage of foreign born from a much more varied number of countries. And it probably is worthwhile to know that information and how that G6PD is present in our current military population. Not necessarily the military of 20 and 30 years ago.

DR. FLETCHER: Thank you very much. As I understand Dr. Schaffner will bring the committee together and we'll have an answer to this question at the end of the meeting.

DR. SCHAFFNER: Do you know when is a good time to have a disease control committee meeting?

COL FOGELMAN: I think we could --

DR. FLETCHER: We will have committee breakouts.

COL FOGELMAN: We can either do it --
DR. SCHAFFNER: After 3:00?
DR. FLETCHER: After three.
DR. SCHAFFNER: Okay.
DR. FLETCHER: Late this afternoon.
COL FOGELMAN: Okay. I was going to say we could either do it later today or tomorrow morning.
DR. SCHAFFNER: Let's do it later today.
COL FOGELMAN: Do you want Dr. Ockenhouse to be there or --
DR. FLETCHER: Sure.
COL FOGELMAN: Will you need more information from him?
DR. SCHAFFNER: If he's around, fine. Otherwise --
COL FOGELMAN: Okay.
DR. FLETCHER: Thank you very much.
COL FOGELMAN: Can I come and get you when they meet?
MAJ OCKENHOUSE: Sure.
COL FOGELMAN: Okay.
DR. FLETCHER: Dr. Broome?
DR. BROOME: I'm happy to participate in the disease control committee meeting, but I'm a

little unhappy that we don't have some pertinent numbers such as of the military African-Americans tested what proportion have absent or very low versus 10 percent residual G6PD activity. What is the frequency of hemolytic anemia reactions in troops who have received your 45-milligram regimen, you know, any ability to balance levels of malaria risks versus alternate regimens. You know, I think the committee can only go so far without provision of some fairly obvious data.

DR. FLETCHER: I certainly agree. I think this would be a step-wise thing, whatever is necessary --

COL FOGELMAN: Right.

DR. FLETCHER: -- to have the proper answer.

DR. SCHAFFNER: We note that they weren't presented today and we've had this presented to us at least once before, but that may become the focus of our discussion this afternoon.

COL FOGELMAN: Certainly if you need more information you don't have to have the final answer by the end of this meeting.

DR. FLETCHER: For everyone's information,

we are trying to answer these questions progressively but not too immediately to do it improperly.

Yes, sir?

DR. DeFRAITES: This is Bob DeFraites. I guess the only thing close to sort of observational study of this problem -- at Fort Drum, New York in 1993 we had the experience of prophylaxing a large number of troops unscreened for G6PD deficiency. We prophylaxed them with Primaquine 15 milligrams a day for 14 days. This was not directly-observed therapy and what we set up was a -- was at least notifying the health clinics at Fort Drum for these approximately 6,000 troops that got this Primaquine. The physicians and the physicians' assistants were to be alert for sine dysclorictoris [phonetic] and familiarity with the side effect of Primaquine.

We had referred to us two soldiers with sclorictoris. One of whom had vivax malaria at the time. The other one was a woman in her 20s who had taken two doses and then developed dark urine and stopped taking the Primaquine. That's the only case that we know of. And unfortunately we were unable -- after her hemolytic episode -- we were able to

document hemolysis at the time, but were unable to follow up with her individually to see if she really had a deficiency or not, but we assume she did.

That's the only case that we know of. The other fellow had vivax malaria and we don't know whether he was G6PD deficient either. He was white and she was black.

That's the only experience we have that has any kind of numbers.

DR. FLETCHER: Thank you.

DR. DeFRAITES: But that was an unscreened population.

COL FOGELMAN: Any other questions?

(No response.)

COL FOGELMAN: Okay. Thank you very much.

Our next speaker will be Dr. James Writer who is an epidemiologist in the Division of Preventive Medicine at WRAIR and he'll be talking about a study that he's recently performed on a predeployment hospitalization patters for individuals on the VA Gulf War registry.

Dr. Writer?

MR. WRITER: Thank you, Dr. Fogelman. Actually it's Mr. Writer.

COL FOGELMAN: Oh, sorry, Mr.

MR. WRITER: Okay. First slide, please?

(Slide shown.)

MR. WRITER: I'm going to present this morning a preliminary analysis of a study comparing --

COL FOGELMAN: Could we have the lights?

MR. WRITER: -- pre-war hospitalization rates among two groups of Persian Gulf War veterans. One group that enrolled on the Veterans Affairs Gulf War registry and a second group that had not enrolled.

Next slide, please.

(Slide shown.)

MR. WRITER: The objective of the study is to determine or analyze the pre-deployment health care utilization behavior of registry enrolles and non-enrollees and determine of the behaviors differed.

Next slide, please.

(Slide shown.)

MR. WRITER: At this time a number of independent review committees have concluded that there is no unique syndrome associated with service

in the Persian Gulf. And others have shown no adverse impact on post-war mortality or on hospitalization rates.

However, some veterans and their families feel that many of the Veterans illnesses are associated with their war service.

In reality a relatively small number of Army war veterans, about 7 to 10 percent as of February 1996, have enrolled on the VA's registry. Why someone enrolls is probably a complicated decision process involving the presence of signs or symptoms, a perception of exposure to risk, actual disease and a willingness or a need to access the health care system.

In this study I examined one small part of the process. Health care utilization behavior before deployment. I believe this is the first study to examine the pre-war behaviors and their associations with the perceived post-war adverse health effects.

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(Slide shown.)

MR. WRITER: The VA registry was established in November 1992 by public law. And it

was called the Persian Gulf War Veterans Health Status Act. The registry is open to all veterans, reserve, national guard, and prior active duty with health concerns that they attribute to Gulf War Service. Current active-duty soldiers have also been enrolled on the registry but they are not well represented.

Using its own data and data supplied by the Defense Manpower Data Center or DMDC the VA identified and assembled a database of enrollees and eligible non-enrollees. These data include date of birth, sex, rank, race, length of service, date of enlistment, marital status, dates of deployment and return from the Gulf and data extracted from the clinical evaluation of the patient at a VA health care facility.

The VA data was matched to and merged with pre-war hospitalization data obtained by WRAIR and from the U.S. Army's individual patient data system located at Fort Sam Houston in Texas. These data included date of admission and up to eight diagnoses for each admission.

The VA stripped off all identifiers before supplying us with the analysis data set.

Next slide, please?

(Slide shown.)

MR. WRITER: Since only active-duty hospitalization records were available the eligible population was restricted to just active-duty and prior active-duty Gulf War Veterans. Those who enrolled on the registry had to have appeared on the enrollment date base by February of 1996. All enrollees are self-selected. The comparison group, the non-enrollees were Gulf War Veterans who had not enrolled with the VA, but who were on the DMDC employment roster. The comparison group was randomly selected from the non-enrolled veterans and three enrollees were selected for each enrollee.

Next slide. please?

(Slide shown.)

MR. WRITER: All admissions to Army hospitals occurring up to 10 years before the deployment were included in the analysis. All admissions were eligible. For example, if a soldier had come in three times complaining of low back pain each of those admissions was counted. For each admission, though, only the first listed diagnosis was analyzed. That admission most likely describes

the reason for the hospital stay.

Next slide, please?

(Slide shown.)

MR. WRITER: In this study enrollment on the registry was treated as a marker of past health care system utilization. And graphically you can see how this study was constructed.

Enrollees and non-enrollees were selected in February of 1996. The study period of interest, however, is the period between enlistment or up to 10 years before deployment through to deployment to the Persian Gulf. And looking at in there are the hospitalizations that occurred during this period.

Next slide, please?

(Slide shown.)

MR. WRITER: The two populations were compared for differences in demographic makeup and for time in the Gulf using Chi-square tests. Frequency of admission was also examined and differences evaluated using a non-parametric test, using person years on active duty before deployment. Again, up to 10 years before deployment as a denominator and the number of admissions as a numerator. Admissions rates were calculated and

relative risks determined.

Finally, no control -- or finally, control for potential confounders was done using a multi-variate poisson or progression model and STATA Version 5 was used for all analyses.

Next slide, please?

MR. WRITER: Looking at the count of individuals and cumulative person years you see that about 11,000 prior active-duty soldiers had enrolled on the registry and there were about 32,000, 33,000 who were not on the registry. In both the population and the person years if a portion contributed by those on the registry and not on the registry is about the same, 25 percent versus 75 percent; roughly 25 versus 75.

In both groups they had spent about five years on active duty before they were deployed.

Next slide, please?

(Slide shown.)

MR. WRITER: In comparing the two groups there were small but statistically significant differences in the age distributions. There's no different in the -- or at least no statistical difference in the distribution within the sex

groups.

Next slide, please?

(Slide shown.)

MR. WRITER: There was a statistical difference in the marital status categories. As you can see here, among those who are single the two groups are about the same. However, in the married and the no longer married groups you can see some very different proportions between those on the registry and those not on the registry.

There was also a statistical difference in the rank group with the junior enlisted -- a proportion of the junior listed higher on the registry than not on the registry and the opposite for the officers.

Next slide, please?

(Slide shown.)

MR. WRITER: In race and in time of Gulf there are also small, but given the size of our population, statistically significant differences in the distribution in these two categories.

Next slide, please?

MR. WRITER: Thirty-one percent of the reported admissions were in the registrants.

Whereas the registrants only make up about 25 percent of the total population. That's -- let's see, 6,600 admissions in the registrants versus 15,000 admissions of those not in the registry.

Thirty-six percent of the enrolles had had an admission while only 31 percent of the non-enrollees had had an admission. And enrollees also had a higher mean number of admissions than the non-enrollees.

Next slide, please?

(Slide shown.)

MR. WRITER: The enrollees also had a higher crude admission rate than the non-enrollees. 119 per thousand person years versus 92.3 per thousand person years. That translates to a relative risk of 1.3 with rather narrow 95 percent confidence intervals.

Just as a point of reference in 1995 the admission -- the annual admission rate for active-duty army was about 130 per thousand person years. Of course, those include soldiers who are in garrison or may not have been deployable.

I also just took a quick look to see -- look at people who had ever been hospitalized versus

those who had never been hospitalized and the relative risk if you're just looking at ever hospitalized versus never hospitalized is 1.6 with a lower confidence interval of 95 percent confidence interval of 1.13.

Next slide, please?

(Slide shown.)

MR. WRITER: The gap between admission rates for enrollees and non-enrollees increased as the number of admissions increased. Among those with one admission enrollees were slightly more like to have been admitted while those who had more than five admissions you can see they're 85 percent more likely to have been admitted.

Next slide, please?

(Slide shown.)

MR. WRITER: Stratified relative risks revealed greater differences in hospitalization rates as ages increased. There's no -- little or no difference in the stratified relative risks for males and females and also little or no difference in stratified relative risks when you look at it by marital status.

Next slide, please?

(Slide shown.)

MR. WRITER: Differences between rates were greater in the senior enlisted and the officer categories. That in the junior enlisted -- I don't know if we can focus this a little better?

In the race categories you can see blacks had a -- the difference in hospitalization rates for those on the registry and not on the registry are not as different as for whites and for other and for time in the Gulf for whether they're more than 120 days or less than or equal to 120 days the admission rates were similar. I shouldn't say the admission rates, but the relative risks are similar in the two categories.

Next slide, please?

(Slide shown.)

MR. WRITER: The multi-variate poisson model you can see what was put into the model here, essentially all the variables were forced into the model. That gave us a relative risk of 1.27 which is very similar to the crude relative risk 95 percent confidence levels again, very narrow, 1.23 to 1.31.

Next slide, please?

MR. WRITER: Using the same poisson model

adjusted relative risks are calculated for each of 16 major ICD-9 diagnostic categories and they are ranked here according to the highest relative risk to the lowest relative risk. And you can see the top five categories are signs, symptoms, ill-defined conditions, endocrine, nutritional metabolic diseases and immunologic disorders, diseases of the musculoskeletal system, connective tissues, diseases of the nervous system and sense organs, and mental disorders, and then followed by circulatory, digestive, respiratory and then further down.

Next slide, please?

(Slide shown.)

MR. WRITER: The next two slides -- or on the next two slides the diagnostic groups are further broken down in adjusted relative risks for each group presented. These are the top 25 admissions based on the total number of admissions.

This first slide has the first 12 reasons for admissions, and the bolded categories -- although that may be difficult to see what's bolded and what's not bolded from where you're sitting. It was supposed to show the significant relative risks, picked out a few of the higher ones, sprains and

strains of the joints of adjacent muscles, osteopathies, dorsopathies, other diseases or the respiratory track, rheumatism excluding the back, symptoms with no other diagnosis made and neurotic personality and other non-psychotic disorders are probably the leading ones in this group.

Next slide, please.

(Slide shown.)

MR. WRITER: On this slide we see the next 13 leading reasons for admission. The highest one here, disease of the esophagus, stomach, and duodenum. I think the next highest one after that is pneumonia or influenza or diseases of the veins and lymphatics and other diseases of the circulatory system.

What you note on both of these slides is that conditions with little subjective component to the diagnosis like pregnancy and fractures, complications in labor and delivery and complications related to pregnancy have relative risks, but they do not significantly differ from one.

Next slide, please?

(Slide shown.)

MR. WRITER: Conclusions. The preliminary analysis I've just presented examined the pre-deployment hospitalization experiences of Persian Gulf veterans who had enrolled on the VA's Persian Gulf War registry and a comparison group of veterans who have not. The enrolled veterans as you've seen had approximately 30 percent higher overall rate of pre-deployment admissions than the non-enrolles. And the five relative risks -- the highest relative risks I've already talked about and you see them here on this slide again.

Next slide, please?

(Slide shown.)

MR. WRITER: There are a number of potential biases or limitations though that I need to discuss. By using all admissions there may be a chance of overestimating the impact of specific diagnoses that are repeated often. However, since this was primarily a study of health care utilization this was necessary and should not affect the overall pre-war rates.

There's also a possibility of under estimating admissions. Since I was certain of getting only Army admissions -- now, soldiers who

are not admitted to Army hospitals do appear in the IPDS patient record system. Especially when the soldier or the treating facility is seeking reimbursement for treatment. Therefore, I believe that nearly all the admissions were captured.

And when dealing with specific diagnoses, miscoding, and the using of the first diagnoses only may alter the result of the sub-group analysis. I had no control over the coding process and I decided to use the first diagnoses since it makes the analysis manageable and should also be the more specific diagnoses within that list of eight potential diagnoses capturing the truer reason for the hospital stay.

Of these potential baises, however, there's no reason to believe that they would have been more or less likely to occur in either of the two study populations.

Next slide, please?

(Slide shown.)

MR. WRITER: These two limitations are of greater concern: Soldiers on the registry have probably left active service while those in the comparison group could still be on active duty. It

is possible that illnesses or other disabilities may contribute to soldiers leaving active duty and then enrolling with the VA. Soldiers who have stayed may differ in some way.

This awaits probably a similar analysis of the comprehensive clinical evaluation program data. Those data weren't available when we started this project.

Another issue is whether or not some of the comparison group had enrolled on the CCEP program resulting in a misclassification bias. And if so, what effect that would have.

Most likely if hospitalization rates are higher among those who enrolled on a post-deployment registry whether it be the CCEP or the VA registry then the relative risk presented here is a conservative estimate of the association between health care utilization and enrollment.

Next slide, please?

(Slide shown.)

MR. WRITER: The study does have a number of strengths I'd like to point out also. Nearly all the active duty or prior active duty soldiers who had enrolled with the VA by February of 1996 are in

this study. The study -- the two study groups were deployed to the Persian Gulf so both should have a similar baseline health status.

We had a large study group, gave us good statistical power to be able to detect differences if and when they existed. And because of the way health care was delivered and paid for, most, perhaps approaching all hospitalizations have been captured.

And finally the results are probably plausible.

Next slide, please?

(Slide shown.)

MR. WRITER: And then picking up on the plausibility point, because of pre-existing medical conditions or because of behavioral traits as listed here on the slide, some people may be more likely to use the health care system. And that pre-deployment behavior it's not unreasonable to expect may continue over to the post-deployment phase of their life.

It appears that there is an association between being a heavier user of the health care system and enrollment on the VA's post-war registry

and that the association is stronger for some diagnoses than for others. But the relative risks, while significant, are not really all that large.

Next slide, please?

(Slide shown.)

MR. WRITER: The question that this study then poses is, can knowledge about health care utilization before a deployment be used to identify soldiers who may be at risk of future illnesses or health complaints.

This slide shows possible mechanisms that could be employed. One more comprehensive pre-deployment medical surveillance or making the preparations for overseas movements, screenings a more complete medical screening.

But whether either of these would have any impact or have a significant enough impact to warrant application of these both administratively difficult and expensive options is open to debate. And the population of attributable risk here is only 7 percent, so health care utilization probably is not a very strong predictor of future behavior. And the reasons for seeking health care are so multi-factorial that it would be extremely difficult to

quantify them.

That's it. I'm open to any questions or comment.

DR. FLETCHER: Thank you, Mr. Writer. A question about your term "symptoms" can you qualify further, a couple of times you just had "symptoms"?

MR. WRITER: Right. It's an ICD category. There's one of the major categories of 16 or so, I think, is just symptoms. People who come in and say that they have headaches, they're dizzy, they -- stomach pain, they have -- that does not result in a diagnosis being reached. That's pretty much what the symptoms category is. Something the patient is complaining about where no diagnosis can be assigned to it.

DR. FLETCHER: Yes.

DR. SOKAS: I was wondering what proportion of the people on the VA registry have no complaints? They just kind of registered because they wanted to be --

MR. WRITER: The VA says about 20 percent or so of people on the VA registry do not get a diagnosis. If they are coming in and do -- now, I'm not saying they don't have complaints, but they're

not getting a diagnosis. They may present with a complaint but nothing is found that diagnosable. I don't have a sense -- or I don't have the exact number of how many had no complaints but are coming in just to enroll. That I don't have the number on.

CAPT CUNNION: I'm Captain Cunnion ESUHS. As being once a part of the CCEP program many of the people had multiple diagnosis on hospital admission. In your study did you look at the difference between the number of diagnosis give on admissions between the two groups?

MR. WRITER: No, I didn't. I didn't look at -- for each admission I didn't look at the number of diagnoses. No, I didn't do that.

DR. COWAN: David Cowan, WRAIR.

DR. FLETCHER: Yes.

DR. COWAN: Two questions, were you able to look at the diagnosis they received at the VA registry?

MR. WRITER: I have those. And I didn't look at them in this analysis, but I have, I believe, three diagnoses -- up to three diagnoses I would have gotten from the VA when they were

evaluated there.

DR. COWAN: That might be an interesting avenue to pursue.

MR. WRITER: It would be interesting to see if we could tie it together what was going on before and what they are presenting with or being diagnoses with after. But I didn't go that far with this yet.

DR. COWAN: Next question.

MR. WRITER: Yes.

DR. COWAN: You mentioned the CCEP data were not available when you started.

MR. WRITER: Correct.

DR. COWAN: Are you now working with the CCEP data?

MR. WRITER: No, actually I haven't gone back to it to incorporate that into it. I think Commander Gray's group is working with doing a similar analysis with the CCEP if I'm correct. Is that correct, Commander? Yeah, so I'm probably not going to pursue that for just the Army group since I believe their group is going to be tri-service.

DR. COWAN: Thank you.

DR. FLETCHER: Dr. Sokas?

DR. SOKAS: Did I understand you correctly

--

MR. WRITER: Yes.

DR. SOKAS: -- you analyzed the admission diagnosis? Did you also look at the discharge diagnosis?

MR. WRITER: So that would have been the discharge diagnosis. It's not the chief complaint. It's the actual discharge diagnosis. The first one of the eight that are available.

COL JONES: Jim, very nice presentation. Colonel Jones, CHPPM. I have two questions. The first is, of those individuals who registered with the VA, how many of those people were hospitalized for those conditions other than for evaluation; do you know?

MR. WRITER: That I don't know off hand. I don't know that I had that information. I'd probably have to go back to the VA to get that. Whether or not after the VA did their first look at them and decided to hospitalize them for further evaluation that I don't know.

COL JONES: The reason why I ask is my impression of these complaints is that most of them are not the type of thing that you would end up

being hospitalized for.

MR. WRITER: Uh-huh.

COL JONES: And therefore the better predictor in terms of health care utilization prior to deployment to the Persian Gulf may be out-patient visits because these are minor complaints. And so if there's going to be a pattern it's not going to be amount hospitalizations but rather among the types of minor complaints that they continue to have afterwards if there's a relationship. Do you know if anybody is looking at that?

MR. WRITER: No, that would be extremely difficult to look at the out-patient visits prior to deployment. Probably couldn't do it in a group this size, you may have to do a much smaller case control study or something where you could have a manageable number of patient records you could go through and look at each of their out-patient visits. Even then you would probably miss some of them.

But, no, I haven't looked at out-patients. You're right, though.

COL JONES: It seems to me that everybody has a record. Those are archived someplace so that you could actually do a randomized comparison

between cohorts of those who deployed and didn't. Thank you. Very excellent presentation.

DR. FLETCHER: Dr. Gwaltney.

DR. GWALTNEY: Yeah, I just want to -- I had the same comment and I realize it's more difficult, but I congratulate you and Dr. Kelley on this study. I think it's very important.

MR. WRITER: Thank you.

DR. GWALTNEY: And it would be interesting to go on and look at out-patient records at least in a smaller group or whatever you could do to see if that confirms or extends the differences that you observed.

MR. WRITER: Yeah, I think that would e very interesting to find out because this -- we're only getting the serious complaints here. Serious enough that if someone felt they needed to be hospitalized and maybe the unhospitalized complaints actually indicate what's going on with the patient before they deployed or the person before they deployed.

DR. GWALTNEY: There may be clues there also in terms of screening and picking up these people and helping them in some way.

DR. FLETCHER: Dr. DeFraites is next?

DR. DeFRAITES: Yeah, this is Bob DeFraites. Jim, a great presentation. I am concerned though about this one bias about not being on active duty. You showed that persons who show up on the registry are older than those who didn't. And also, if we don't know if they're still on active duty one could easily -- I mean, one big confounder would be if there are conditions that caused this person to leave active service, that person may have been more likely to seek care through the VA system and also sign up on this registry.

So if there's any way to determine the active duty status of these two groups presently when you do it, at least through 1996 and whenever the cut off date, that I think would add a great deal to understanding what this might mean.

The second comment is, I maybe misunderstood the implication, but you certainly appearing on the VA registry is voluntary. I thought I heard you also say that getting admitted before the Persian Gulf War was also voluntary in a sense that seeking or demanding care -- and I think

the admission data are fairly powerful in the sense that you do have quite a bit of a filter in a sense that a physician has to admit you to the hospital. Somebody has to sign the admission order to get you in the hospital so I don't think it's strictly self-selection.

MR. WRITER: Yeah, I didn't mean to have it sound like that, that you were self-selecting for admission before. There's a component of it that's self-selection that you're coming in complaining, perhaps asking for a further evaluation that you would get as an outpatient. But you're right, I mean, the physician is the gatekeeper and that's not going to be as self-selected as appearing on the VA registry.

DR. DeFRAITES: I think they could. The patient could still exert some pressure, but there is a filter.

MR. WRITER: Right.

DR. FLETCHER: Dr. Trump?

DR. TRUMP: As sort of a related concern and with the comparison group, what was their active duty status?

MR. WRITER: The comparison group could be

both prior active duty and current active duty.

DR. TRUMP: Okay. That would be -- I think that is one big concern with the analysis is if -- you know, if they are still on active duty, then their primary source of registration is through the CCEP, the active duty program.

MR. WRITER: Right. Uh-huh.

DR. TRUMP: And you basically have a large group that could be misclassified.

MR. WRITER: Right.

DR. TRUMP: And I think it's an important line of analysis but it really is a preliminary conclusion until we can, you know, combine that --

MR. WRITER: I agree.

DR. TRUMP: -- those two registry populations and look at the total experience.

MR. WRITER: Yeah, I'm curious to see what the analysis, the CCEP data shows. If it shows similar patterns and similar -- relative risks. If somebody knows the CCEP -- the rate of enrollment, I had a number, I thought it was around 4 percent of active duty were getting on CCEP or are currently on. That's not -- also a fairly small number. I don't know of that's correct, though.

DR. DeFRAITES: This is Bob DeFraites again. The number I remember seeing in a report of 18,000 that was published in 19 April, I believe that you're right, that about 4 percent of the unit strengths in 1990. In other words they looked at the cohort, the 695,000 whatever number you choose around that, that about 4 percent have registered for CCEP. I believe that's true.

MR. WRITER: Yeah, so while there is potential for misclassification it probably is occurring kind of --

DR. DeFRAITES: Well, the number is going to be higher now.

MR. WRITER: Right.

DR. DeFRAITES: Every time there's publicity the numbers shoot up. So that number is floating. But, you know, it was 4 percent in -- when the numbers were 18,000 total. Now the numbers are 26,000, I think.

DR. TRUMP: Twenty-eight.

DR. DeFRAITES: Twenty-eight thousand.

MR. WRITER: Twenty-eight. Okay. So probably closer to 10 percent.

DR. FLETCHER: Microphone.

MS. NELSON: Ann Nelson from the AFIP.

MR. WRITER: Uh-huh.

MS. NELSON: I realize why you had to use the active duty for statistical reasons 'cause reservist information would be much harder to obtain, but overall what percent of people deployed are on the VA registry and of those, what fraction are active duty and what fraction are reservists?

MR. WRITER: If my numbers are right, I think there's -- I can only address Army. I think there are around 370,000 U.S. Army troops, reserve guard and active duty who went to the Gulf. About somewhere between 22, 25,000 have appeared on the VA registry. So it's around 7 to 8 percent are on the VA registry.

The VA registry is about 40 percent though reserve and guard, maybe a little more than 40 percent reserve and guard. That's -- I mean, the reserve and guard are better represented on the VA registry than the active duty are.

DR. FLETCHER: Dr. Anderson, do you have a comment?

MR. WRITER: Yes.

DR. ANDERSON: Just quickly, were you able

to look at regional differences at all? The hospital utilization could be different by which VA hospital and where in the region or the country you were early on versus a prior -- you know, subsequent hospitalization.

MR. WRITER: Didn't look at regionalization -- at the regions, especially for the VA. I wasn't looking that closely at the data I had on the VA hospitalization. The in-point there was pretty much were you on it or you weren't on it for this analysis. That could also be true though, even for the Army hospitals whether different patterns or admission in different Army facilities. But, no, I didn't look at that.

MAJ LUDWIG: Yes, Sharon Ludwig at CHPPM. I just want to take this opportunity to put in a plug for the need for out-patient surveillance, regular, standardized, and formalized out-patient surveillance. These suggestions about doing this study without patients is an excellent one, but impossible -- virtually impossible to do because there is no database without patient visits. And if that were put into practice as a standard and I know there are a lot of people working on this and

interested in it even at CHPPM, but it would make deployment surveillance easier, too, because people would be accustomed to doing it. So, thanks for the opportunity to put in that plug.

MR. WRITER: I second that plug.

DR. FLETCHER: Thank you very much. We will move on.

(Applause.)

COL FOGELMAN: Our next speaker is going to be Captain Select Greg Gray who is a researcher -- research epidemiologist at the Naval Health Research Center in San Diego. And he'll be talking about post-war hospitalization experienced by Persian Gulf Veterans. This article was recently published in the New England Journal of Medicine.

CAPT GRAY: Well, thank you very much. Could I have the first slide?

COL FOGELMAN: Could you speak up, Greg?

DR. FLETCHER: Microphone.

COL FOGELMAN: You may need to hold the microphone if you can.

CAPT GRAY: Thank you very much. How's that?

COL FOGELMAN: I think you're going to have

to hold it.

CAPT GRAY: Okay. What I'd like to do today is tell you a little bit about the development of our family of studies.

DR. FLETCHER: Use the big microphone.

(Slide shown.)

CAPT GRAY: Oh, okay. How's this? Okay.

(Slide shown.)

CAPT GRAY: Tell you a little bit about the development of our studies. Go over the studies that have recently been published and also talk a little bit about where we're headed.

Is there a slide changer? Okay.

We initially proposed a very modest study in July of 1993 to compare the post-war hospitalizations among a small cohort of marines with their non-deployed counterparts. Those studies that were met with receptive ears after several months at DOD health affairs who have been the sponsor of this work.

We've had a number of external reviews, the first of which occurred in January of '94. We received funds in April of '94 and had a number of milestones in the interim between that and our first

publication here recently.

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(Slide shown.)

CAPT GRAY: Realizing that these were very sensitive and difficult studies, we quickly asked a number of collaborators to join us. You'll see that we have collaborers here from a number of military organizations, but also from the University of California at San Diego, Dr. Barrett-Connor, in fact, has been with us from the very beginning and the late Dr. Samuel Wishic, and we've also had collaborators from the Department of Veterans Affairs and the EPA and most recently the CDC.

Next slide, please?

(Slide shown.)

CAPT GRAY: We gathered together on a number of occasions with some strawman protocols and really worked out the bugs early on for three exploratory studies and later these developed into four more comprehensive studies.

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(Slide shown.)

CAPT GRAY: The studies have been reviewed by a number of external reviews. They tell me that

our studies have been reviewed more than any others at my institution. The Defense Science Board, this prestigious body, I think in July of 1994 GAO -- we had our own special external review with some very distinguished panelists. And then recently the Institute of Medicine and the Presidential Advisory Committees reviewed our work.

Next slide, please?

(Slide shown.)

CAPT GRAY: Now, when we set about to look at the claims of increased morbidity among Gulf War veterans there were a number of hot pursuit studies already accomplished. This is one Dr. DeFraites led this effort. And what they found was that there was a lot of symptom reporting, but it was very difficult to define outcomes and to define exposures that might be related to those outcomes.

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(Slide shown.)

CAPT GRAY: This study was followed by a number of expert panel attempts at defining a case definition which to this point has not been satisfactory.

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(Slide shown.)

CAPT GRAY: And so we worked from a hypothesis that sort of my area of interest the strep hypothesis and we ventured that perhaps there was an exposure or a series of exposures that might be manifesting in several different ways, different unique diseases much like the streptococcus causes unique syndromes and diseases, some acute and some chronic.

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CAPT GRAY: We looked at our resources and the available data and decided to focus in three areas in exploratory work among active duty initially because it was the data were both surveillable.

We decided to do a survey among people that were reporting a lot of symptoms and that would be the Navy construction workers or seabees. We decided to examine hospitalization and reproductive outcome data from data that were already captured by all medical treatment facilities throughout the world in the Department of Defense.

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CAPT GRAY: Our objectives in these studies were to compare the illnesses infertility symptoms and reproductive outcomes between the Gulf War veterans and their non-deployed veterans of the same era. And what we hoped is that we would find differences that we could link back to the unique exposures or a series of exposure and that these linkages would lead us to more comprehensive studies that we could get to perhaps a biological mechanism.

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CAPT GRAY: Our Gulf War -- in most of our studies our Gulf War veterans are defined as this. If you were in the theater as defined by the Defense Manpower Data Center between 1 August '90 to 31 July '91 for one or more days you were considered a Gulf War veteran. It's a very broad definition.

Non-deployed veterans are if you were not in that theater yet on active duty as of 30 September 1990.

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CAPT GRAY: Our initial studies involved the number of people shown here. Only 1500 in the seabee population, 1.2 million in the hospitalization study -- I'll explain a little bit -- and 1.2 million in a study that's been submitted to the Journal by Doctors Cowan and DeFraites are waiting to hear regarding birth defects.

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CAPT GRAY: At present we have seven active protocols about 18 different projects under these seven protocols that should all lead to one or more manuscripts. We've collected data here in the first series of studies that involve only active duty. This paper is one I'll talk about. This one is submitted. This one is being finalized.

The next step in the family of studies involved examining not only the active duty folks that we've looked at in the first three studies, but also the people that have left the military or who were in the reserve or guard components. And they are much larger.

We intend to look at -- we're in the final processes of a very long -- I think eight month

procedure with the Office of Management and Budget to do a survey among 17,000 seabees.

We've recently acquired data from California to look at hospitalizations -- non-federal hospitalizations in California and to compare Gulf War veterans and non-deployed veterans. And recently we've begun a study of -- a very ambitious study, never been attempted before to link data from seven actively surveilled birth defect registries across the United States looking at birth defects in the aggregate as well as specific diagnoses. We've piloted this in Hawaii and we're working on the linkage software to link it with Arizona which will be a next sampling site.

We also have underway -- it's a little hard to see with that focus, but a large male survey of 16,000 couples. We're at about 46 percent participation rate after the second mailing. And so we're pursuing outcomes here of reproductive outcomes that are hard to get from our other sources of data, mainly infertility and miscarriages.

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CAPT GRAY: This is the paper that was

recently published. You'll note that we have a number of investigators from the Naval Health Research Center, but Dr. Hong Kang from the VA, Dr. Steve Wignall who is formerly -- he's a Gulf War veteran himself and formerly with NAMRU 2 in Jakarta and Dr. Elizabeth Barrett-Connor who is in the room and represents the University of California at San Diego.

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CAPT GRAY: The objectives were to compare the hospitalization risks and identify disease categories that merit further investigation.

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CAPT GRAY: This is a retrospective cohort study using data that were captured for other purposes. Our outcomes were examined from one 1 August '91 to 30 September 1993. And we did look at data before the Gulf War as well, and I'll explain that in a moment.

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CAPT GRAY: We combined demographic

information that were available to our institution and data from hospitalization files to run these analyses.

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CAPT GRAY: We chose two classifications of outcomes. We examined the risk factors for any cause of hospitalization during the time period of interest and also we examined -- we performed modeling for 14 major ICD9 categories. There are 17 major categories in the ICD9 catalog. Doctors Cowan and DeFraites are actually examining the other three which are reproductive in nature.

Because of the size of our modelling the 1.2 million people, we had some trouble initially with cost proportional hazard modeling so we used the logistic regression approach. And because of the assumptions in that modeling we divided the time period up into three unique periods: five months in '91 right after the war, all of '92, and eight months of '93.

Our scientific advisors recommended that we stop analyzing the data at that point because of the high attrition from the regular active duty

population that we had. As of this time at the last period we had about 43 percent attrition from service and the thinking was that we were -- we were having more potential bias with people attriting.

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CAPT GRAY: These are the 14 categories we examined in these analyses over three time periods. You'll see that they're very broad and pretty comprehensive with respect to the span of morbidity.

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CAPT GRAY: Initially we worker with these covariates as we found that the two populations -- Gulf War veterans and non-deployed veterans -- were different statistically for each of these demographic variables, moreso for gender and for age, but certainly all of these were statistically important and different.

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CAPT GRAY: We next examined the pre-war hospitalization experience of these two large cohorts. We had data to this point for all three

services, but the tri-service database was constructed at this point so we could not combine data from the other -- from the Army and the Air Force beyond that. And we found that if you divide the time periods up into quarters that there was a difference in risk with Gulf War veterans being less likely to be hospitalized before the war than their non-deployed veterans. And we wondered if this was a characteristic that was true over time for them.

Having no way to examine the three services we examined only the Navy and Marine Corps subgroup in our two cohorts and what we found is that the risk was not apparent beyond about this point. And so we think in consulting with folks from the Institute of Medicine that this is a transient selection effect and we tried to adjust for it in the modeling that ensued. Could I have the next slide?

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CAPT GRAY: We did that by creating a new covariate, pre-war hospitalization for the period just before the war, coded it one or zero.

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CAPT GRAY: Looking at the outcome of any cause of hospitalization we found that in general females were more likely to be hospitalization than males; caucasians than other races; army personnel; married personnel; personnel of lowest ranks and salaries; and medical workers in contrast to the other eight different occupational categories.

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CAPT GRAY: The odds ratio, though, for the Gulf War service co-variate was not important in these three models. Here you see that the odds ratio includes one in the confidence interval. So there didn't appear to be a difference in this model being a very powerful one with respect to Gulf War status.

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CAPT GRAY: We then looked at the 14 categories over three time periods and here you see some of those data. There was no difference here with respect to -- Gulf War veterans were not at increased risk. This is an odds ratio. Anything above the bar means that Gulf War veterans are at

increased risk. But they weren't at increased risk for infection and parasitic diseases, however, there was an increased risk for neoplasms in the five-month period of 1991. And there was an increased risk for diseases of the blood in the 12-month period in 1992.

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CAPT GRAY: So then we looked at those categories and abstracted the tenth most common diagnoses in those categories which for the most part accounted for between 60 some and 100 percent of the outcomes in those categories.

And we -- here you see a number of them, not all of them, but you'll see that the majority of the admissions in these categories were for benign conditions. There is the tenth one, I think, is testicular cancer. It's mentioned in our paper.

What we found, though, is that what we think is going on is that these people had various fatty tumors or whatever that were deferred until they came back. We saw no evidence of increased risk in 1992 or '93 for -- the one we're most concerned about and that was testicular cancer. So

we think it's either occurred by chance or certainly it doesn't make sense with respect to latency period and known carcinogens. A five-month window is biologically impossible.

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CAPT GRAY: Regarding the diseases of the blood, we found this very interesting, but the most common diseases contributing to this difference between Gulf War veterans and non-deployed veterans were for diseases or anemia. And what we found through Doctors Cowan and DeFraites work was that there was a baby boom among women after the war and we thought, well, perhaps this is pregnancy related and sure enough when we removed all pregnancy related admissions this went away. So these we think were due to anemia of pregnancy.

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CAPT GRAY: We also looked at some more categories and found that mental illness disorders and diagnoses were elevated in both time periods, '92 and '93.

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CAPT GRAY: And when we looked at that we found that the majority of these differences were due to alcohol- or drug-related conditions. Certainly this is consistent with what we know from Vietnam. That is that veterans -- some veterans deal with the stresses of war through alcohol and drugs.

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CAPT GRAY: Finally, in our last group of categories we found a slight increase for five months of '91 for genital urinary conditions.

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CAPT GRAY: And examining that we found a number of inflammatory conditions that were gender specific for women and we hypothesized that well, perhaps the availability of medical care in the Gulf caused some women to at least defer care until they returned to the states and saw their gynecologist.

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CAPT GRAY: One of the potential biases in this study would be since we're only following

active duty what if our sickest people were getting out more quickly among different cohorts it would -- it would cause some problems.

So we looked for evidence that perhaps Gulf War veterans were sick and getting out more quickly than their non-deployed veterans. We found an overall attrition rate from regular active duty to be higher for the Gulf War veterans, but when we examined the causes for this, we did not find an increased risk for Gulf War veterans to be discharged for medical disqualifications or to be cause -- as Dr. Kang's paper has shown -- more credibly for death.

And there's a great incentive for a service person to report medical conditions before he is separated because of the medical compensation that's available and long-term care. So we think that we can be pretty confident that they are not experiencing increased morbidity at least at separation.

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CAPT GRAY: Limitations of the study are a broad classification system. One or more days in

the Gulf and certainly that included the whole Gulf War theater which is quite broad.

Another limitation is that we only looked at active duty personnel and the conditions with a long latency. We just wouldn't have opportunity in these data to examine such conditions associated with Gulf War service.

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CAPT GRAY: Some of the strengths are we had tremendous statistical power to detect differences. We think we have a high capture of percentage of hospitalizations as it really is difficult for an active duty person to be hospitalized outside of the DOD system for purposes of accountability and also costs.

And finally we think that hospitalizations are a harder outcome, if you will, than self-reported symptoms. So, in a way, we screen out in this sort of drill the more severe manifestations of illness.

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CAPT GRAY: We conclude in this paper that

-- or in summary of the paper we've looked at 14 diagnostic categories and any causal hospitalizations over three time periods and Gulf War veterans were at increased risks in five of these 45 models. But they were not consistent over time, the increases, and we think they can be explained by deferred medical care, a baby boom, and conditions known to be associated with war.

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CAPT GRAY: So we conclude that during the two years after the Persian Gulf Wart, 25 months, there was no excess of unexpected hospitalizations among Americans who remain on active duty after serving in that conflict.

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CAPT GRAY: We have some follow-on studies on these data. Right now we are screening hospitalizations now comparing Gulf War veterans and non-deployed veterans for 77 diagnostic codes at the Centers for Disease Control in another forum have selected most likely to detect emerging illnesses.

We are also analyzing more comprehensively

through 10 different outcomes the mental illness diagnoses to see if we can detect specific risk factors for some of these.

And as Mr. Writer has pointed out, we're doing a study of the 697,000 the entire Gulf War veteran cohort looking at risk factors for registering an either CCEP or VA. I believe our latest count was 62,000 people have registered in either one of these. About 876 have registered in both.

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CAPT GRAY: Now I'd like to do a little commercial for our team here and to tell you a little bit about more of the things that we are doing. We have about 25 folks here that are now very familiar after a couple of years with the complex databases. Something that is -- the learning curve is rather steep.

We have appropriate information processing in our center with a number of mainframes and desktop PCs and we have full collaborations established with a number of universities, the Centers for Disease Control, as I mentioned, and EPA

and the VA.

We also have a clinical specimen bank that's from one of our seabee studies that may be used to test infectious disease-related hypotheses as they arise in the future.

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CAPT GRAY: Recently the Institute of Medicine has endorsed our seven main studies and recommended that the DOD continue to support them.

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CAPT GRAY: We've recently received 21,000 SSNs from the deployment surveillance team. These SSNs represent people that were within 50 kilometers of Khamiseyah where ammunition has been destroyed that belonged to the Iraq's arsenal. And we're examining their post-war hospitalizations experience with other Gulf War veterans who were not within that 50-mile radius.

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CAPT GRAY: We've been asked by Dr. Joseph in addition to the reproductive outcomes to look at

one specific reproductive diagnoses and it's called Golden Horror Syndrome and we have a paper that's making it's way through internal review at this time examining risk factors for that in a controlled fashion.

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CAPT GRAY: This is sort of out-dated, if you will, but a summary of where we are. We've had one paper that's published. We have three more that are either in journal review or are about to be. We have -- we've published the technical bibliography of 1700 citations related to the Gulf War and we've got now I think 19 abstracts, we just submitted eight more for public forums. I understand that there will be another public forum at APHA this coming year.

So we're moving along trying to get this literature out as fast as we can to the scientific community.

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CAPT GRAY: And what we hope is that these studies in aggregate with other federal studies like

those at this institution and the Centers for Disease Control and certainly our counterparts or colleagues in the other federal and non-federal institutions will help answer questions like these in the future.

Thank you very much.

DR. FLETCHER: Thank you.

COL FOGELMAN: Could we have the lights.

(Applause.)

DR. FLETCHER: Maybe Dr. Elizabeth Barrett-Connor would like to make a comment?

DR. BARRETT-CONNOR: Just to say it's a pleasure to work with Greg and his team. They're really terrific.

DR. FLETCHER: Thank you. Dr. Baker?

DR. BAKER: I thought that was a fascinating presentation. Are there any data that you can get or have you analyzed on length of time in the Gulf so that you could look for sort of dose response effects?

CAPT GRAY: Dr. Samuel Wishic interestingly enough proposed that several years ago and we have done that to a limited extent in one study, the study that's been submitted to a leading journal

right now has some data with respect to dose response. We are looking at individual time periods of exposure. I think we used quarters during about -- you know, the one-year period from storm and shield and other studies. So, although we didn't include that in this modeling, we are in additional studies.

DR. FLETCHER: Dr. Allen?

DR. ALLEN: Given what I have heard about the so-called Gulf War syndrome or illness which largely centers around non-specific illnesses, fatigue, depression, certainly mental aspects and as well as neurologic aspects of ill-defined conditions, it's fascinating to see that none of this got picked up in the post-war hospitalization which leads me to suspect that maybe these people preferentially have not stayed on active duty, have left the military or were in the reserves. I'm just speculating that you may have been looking at a group of people that in fact didn't have, you know, at the point that you were looking at were not at high risk for whatever is going on.

CAPT GRAY: Well, it may be true. We have one study that includes 697,000 where we have

compared people that have registered in either the CCEP or VA and the risk ratio as I recall in the cost prevertial hazard modeling adjusting for a number of covariates -- or excuse me, it's logistic regression modeling, was only 1.2 for reservists. So only a 20 percent more likelihood that they would register than other active duty components. But that's preliminary, but I -- you know, I think a number of people observed it and perhaps some of the reservists are at least participating in CCEP or VA more often than their counterparts.

DR. FLETCHER: Other questions, comments?

(No response.)

COL FOGELMAN: Let's take a break.

DR. FLETCHER: Thank you, Dr. Greg.

COL FOGELMAN: I'd like to take a break until 12:00 and then we'll come back and have a working lunch at that point.

Please try to take a look at that before 3:00 as well as looking at the executive summary so we can discuss that at about three when we break out into our executive session. I'd appreciate it.

(Whereupon, at 11:47 a.m., a brief recess was taken.)

A F T E R N O O N S E S S I O N

(Time noted: 12:10 p.m.)

COL FOGELMAN: Okay. We're going to have a few activity reports today from people who have been doing some things since our last meeting. And our first speaker is going to be Dr. Dennis Perrotta who will talk about the effects of low-level exposure to chemical agents.

DR. PERROTTA: In late June the Environment Committee of the AFEB was asked to take a look at one very specific question as a result of some of the chemical weapon issues that had been brought up in the public and since that time we've heard an awful lot more about them.

The question was this: Are there observable long-term health effects associated with

exposure to Sarin and mustard at concentrations below that needed to cause the acute signs and symptoms or injury that are hallmark as a result of exposure to these.

The methods that the committee used included a literature search, review of available reports, available in the hand of a variety of DOD offices, a discussion with consultants, and a few restricted reports that were available also from DOD.

The consultants that we used included Dr. Sharon Reutter from Aberdeen Proving Grounds, Rogene Henderson who does some inhalation toxicology work and is on the IOM in Albuquerque.

For those of you members who have been on the board for more than a few years, Dr. Meryl Karol who is an immunotoxicologist from Pittsburgh. We knew her as killer Karol for all of her work that she did during our tours of the first couple of meetings we had. And Doctors John Villanacci and Richard Beauchamp toxicologist and physician who are on my staff at the state health department.

I'm going to run through some conclusions and try to do it very quickly, but also completely

as well.

First of all we found that there were no data -- zero data that directly applied to the question at hand. Sort of an interesting finding.

All of the human data and most of the animal data dealt with exposures that were significant enough to elicit the clinical response expected, what in the business they called HIT. So if you were exposed to Sarin and you manifested the classical signs and symptoms of this particular nerve agent -- and I'll tell you about those in a second -- you are regarded as HIT. And the question is, will there be long-term effects for exposures at levels below that required for you to be HIT, if you will.

We found that most investigations were conducted with the country was trying to develop offensive warfare and so therefore they would be focusing on the issues of large doses. What dosages would be necessary to elicit an incompacitating response in the enemy. And so we're not surprised that we didn't find anything in the low-dose literature.

We spent a lot of our effort trying to

determine what was the lowest dose necessary to elicit the clinical response. We learned an awful lot about concentration time or CT that's measured in milligrams per cubic meter times minutes of exposure. But we found that we couldn't identify really a minimal no-observable-effect level or NOEL.

We also learned that exposures are not simple. That temperature, humidity, skin moisture, exposed surfaces, the use of personal protective equipment, pre-treatments, for example, with the use of paradastigmine, wind direction and strength, liquid or vapor state, the activity level of the soldier, host susceptibility and a wide variety of other issues would allow one soldier perhaps standing next to another soldier to be hit while that second soldier was not hit.

Specifically about Sarin, just so that you know and what we found, Sarin is an acutely acting toxic organophosphate that irreversibly binds with acetylcholinesterase. It's first symptoms are rhinorrhea, myosis and chest tightness.

For long-term effects there are multiple lines of evidence that pretty conclusively suggest

that Sarin or GB as it's known in the business is not carcinogenic, mutagenic, or teratogenic.

Now, one of the major findings or the first finding I mentioned was that there was no evidence directly related to answering this low-level question. This information about it being not carcinogenic, mutagenic or teratogenic is that usefulness of higher-dose information that can still provide useful information for answering the question. If it's not carcinogenic, mutagenic, teratogenic at high levels that were tested, then one would expect that it would not pose a threat either at the lower dosages.

So, again, while we weren't provided -- there was no simple book that we could go to, to answer this question. We were able to develop some indirect evidence.

Remembering that this is an organophosphate one of the things that we found had been looked at intensively is something called organophosphate induced delayed neuropathy which is weakness and ataxia eight to 14 days post-OP poisoning. This is seen the agricultural pesticide community on occasion and sometimes this OPIDN ends up going to

paralysis.

Interestingly it was not found in any animal studies or in any man except at dosages of 60 times the LD50 in paratylstigmine protected animals. The chicken was actually the model. I found that whole body of literature pretty darned interesting. But there is evidence to clearly suggest that this delayed neuropathy is not an issue with this particular organophosphate.

There was a body of literature that talked about EEG changes that organophosphates in general caused these kind of changes in monkey and men exposed at high levels.

There were changes, temporal lobe beta changes one year later in men and monkeys exposed to Sarin at high levels. And, in fact, at some men and monkeys exposed at low levels, but repeatedly exposed at low levels they found some changes as well. That gets close to, but it's not quite what we were looking for as far as evidence.

In the report we suggested that more work needed to be done on this. We couldn't -- we didn't feel like we could completely dismiss this just because the doses were not something that -- in the

area that we were interested in.

We found evidence to suggest that there were no other kinds of findings, symptoms, organ system issues along with Sarin except for those that I've just mentioned.

With mustard or HD mustard is a chemical burn and blister agent. It affects mostly moist skin, the eyes and respiratory systems are highly susceptible.

It is an extremely potent alklyating agent. Alklyating the purine basis of DNA leading to the removing of these alkylyated bases. This removal activates enzyme symptoms including one that depletes cellular NAD. I'm hoping that you biochemists are enjoying all of this.

This inhibits glycolysis, activates tissue proteases and results in cellular death. So that's the nickel tour of what mustard does for you.

As an alkylating agent HD is a group one carcinogen. That means there is evidence that confirms that it is a human carcinogen.

In animals pulmonary skin and sarcoma -- had pulmonary cancer, skin cancers and sarcomas have been found. Epidemiologically in human studies of

workers in Japanese weapons factories which represent occupational exposures which are generally higher and not really directly relatable to what we're talking about, but still indicates an increased risk for respiratory cancer and laryngeal cancer in those communities.

Mustard is mutagenic by a variety of tests at high levels. We could find no evidence of teratogenic properties of mustard.

High levels of mustard exposure -- high level exposures to mustard result in respiratory disability besides cancer including shortness of breath, bronchitis, increased risk for chronic respiratory illnesses and infections. But no data that we found suggest similar results for the lower levels that we were talking about. And, indeed, this question remains unanswered.

Ocular burns and injury as a risk factor for long-term ocular disease so that soldiers who had ocular injuries as a result of exposure to mustard ended up with an increased risk of keratitis and intractable conjunctivitis as well as other long-term ocular problems.

However, no evidence was found that without

initial injury that low levels would cause long-term injury. And this is something that's probably worth looking at as well.

As far as skin as an organ system skin is the hallmark target organ and the hallmark measure is a blister. And what I found interesting is that cutaneous cancer often occurs at the sites of the initial scars which is something I had not known before.

However, we found insufficient data to conclude that if exposures lower than that needed to get initial acute injury are associated with long-term skin problems. So we couldn't find any information along those lines.

With your indulgence and because of its importance I wanted to read to you the one statement that our report made about psychological aspects of exposure to mustard.

We said that "A thorough literature review was not conducted on the potential long-term psychological effects of very low dose exposure to mustard." The Institute of Medicine report which is called "Veterans at Risk" and it's an extraordinarily good document that talks about the

exposures of soldiers specifically to -- well, to a wide variety of agents everything from LSD and PCP to mustard and other issues done in the Aberdeen Proving Grounds in the '50s and '60s. So this was an IOM report in '93 that talked about it and had a lot of good information about mustard.

The IOM report conducted a good review on the relationship of exposure to psychological dysfunction as it pertains to experiences of men in chamber and field tests with mustard. Their conclusion was: "Available evidence indicates a causal relationship between the experiences of the subject in chamber and field tests of mustard agents and Lewisite and the development of adverse psychological effects. These effects may be individual, but diagnosable, and may include long-term mood and anxiety disorders, post-traumatic stress syndrome, or other traumatic disorder responses."

We go on to conclude that: While the exposures appear different, there may be significant similarities between the situations within the report, the chamber testings, and those in selected aspects of DESERT STORM. They are both, in our

opinion, outside the range of usual human experiences. The report did not conclude that the chemical itself and its effects on the human body was particularly responsible for the relationship purported.

So since everybody is sensitive about psychological issues I wanted to make sure that we tried to cover that as well.

Finally as far as mustard goes, since it is such a potent alkylating agent we estimated a cancer risk for mustard using basic EPA unit risk measurements. For those of you who like that kind of information the unit risk is 8.5 times ten to the minus two per microgram per cubic millimeter for mustard.

We estimated a five minute exposure at a level which is approximately 10 percent of the observable effect level. And that's a shaky number because I told you that we couldn't find a no-observable effect level -- that's hard to say anyway -- and so we took 10 percent at that because it appears that the slope from zero to the first observable level is very, very steep. And that comes directly from Dr. Reutter who spends her days

at Aberdeen Proving Ground doing this kind of research.

What we came up with is a risk of 5.8 times ten to the minus seven. And to translate that in general terms for every 10 million people exposed for this particular five-minute exposure we would expect 10 additional cancer cases to show up -- I'm sorry, six additional cancer cases, 5.8 times ten to the minus seven. And so our conclusion was is that since we had nowhere near 10 million, as a matter of fact, we thought we were probably fairly generous with several thousand people exposed at this kind of a timeframe. We thought that there would be an undetectable level of increased cancer. You can never say there will be no increased cancer, but we called it undetectable.

And finally the report said that -- and this is just our opinion that further research in the low-dose effects is needed which might include subchronic long-term inhalation, measuring immune and respiratory and -- immune for Sarin and respiratory and eye problems for mustard. And we also thought that there would be some utility to try to determine no observable effect levels for this.

Because not only for the circumstances that we're working under here, but that there are tons of these chemicals that are being demilitarized or are being stored for demilitarization. And there have been plenty of calculations including some done by teams at CDC that suggest that we need to make sure that we have some standards for airborne exposures that can be met by the efforts during the demilitarization.

This was submitted in July 18th after -- this was about a three-week project and since that time you can find it on the Internets on Gulf Link.

That's our report.

COL FOGELMAN: Thank you.

DR. PERROTTA: Are there any questions?

DR. FLETCHER: Any questions for Dr. Perrotta, comments?

DR. ANDERSON: I think there is a current medication on the market for treating mycosis from goides called mustardgen which is in fact mustard gas. And I think there have been some studies at very low levels in those types of patients or in the family members who then help treat the patient.

It's a topical mustard agent. So there is some clinical experience with that.

DR. FLETCHER: Dr. Chin?

DR CHIN: Some clarification. I don't know whether we're talking about documented low levels or undetected levels and I need some clarification of that. Plus, what's the official Pentagon position in terms of was there any quote "exposure" to --

COL FOGELMAN: You're going to hear about two hours on that tomorrow.

DR CHIN: Okay.

COL FOGELMAN: I will defer to the group that's talking tomorrow.

DR. FLETCHER: Yeah.

COL FOGELMAN: What was the first part of the question?

DR CHIN: Well, you were talking about it relates to the second part. Are we talking about undetectable levels or are we talking about low levels, you know?

COL FOGELMAN: We're talking about levels below which symptoms would not appear.

DR. PERROTTA: Right.

DR CHIN: But they should be detectable.

DR. PERROTTA: Below what symptoms would appear of which we believe a very small part of that curve will be detectable. There has to be some otherwise the detection limits of the -- depending on which system that you're using it makes on sense to have equipment out there that can't detect it at levels any less than what you're going to get symptoms at. Otherwise we might as well use biomonitoring.

COL FOGELMAN: I want to just thank again Dennis and the group that he put together working on this and the hundreds of hours that they literally spent putting this report together. And I know Health Affairs, Dr. Joseph, in particular, was very pleased with the results. So, this is --

DR. FLETCHER: I'll ditto that. It was done in a very short period of time and Dennis should be applauded.

(Applause.)

COL FOGELMAN: Our next report will be from Dr. Allen on the vaccine recommendations that were made based on the current bio-warfare threat.

DR. ALLEN: Thank you. This will be very brief. You all have as a handout AFEB (15-1a) dated

November 8th, 1996 which is a memorandum for the Assistant Secretary of Defense Health Affairs on the recommendations from the AFEB. This was developed after a briefing and discussion that the disease control committee or as many of us as could be mustered on October 31st at USAMRIID.

We reviewed current information about biological warfare agents expected or suspected distribution and potential risks. Most of this is classified. But following the review as well as review of available vaccines, vaccines in preparation and other potential defense measures we came up with a list of six recommendations to the Assistant Secretary that we believed were high priority and should be followed through.

I'll just summarize these quickly. First we endorsed the proposed Department of Defense implementation plan for anthrax vaccine using the current vaccine protocol which is a multi-stage immunization effort.

There has been -- there was a little bit of data presented -- a small amount of data presented on an accelerated vaccine schedule, but not enough that we felt we could make a firm recommendation on

it and we encouraged the department to continue studies to obtain additional information about the immunogenisity of the anthrax vaccine using the accelerated schedule.

Second there is an investigational botulinum toxoid vaccine. It's -- we had discussions about whether there was sufficient information and whether we could work with the Food and Drug Administration for licensure at this point. The potential for a limited type of licensure which the FDA does not do. We've also discussed and we encouraged the Department to continue their discussions with the Food and Drug Administration to try to facilitate the licensure of this vaccine. We feel that this is a very important one because of the potential threat for this agent and the fact that without a licensed vaccine any use of it involves -- for deployed troops involves obviously its use as an investigational agent and that's -- that's very difficult.

Third, because of the potential characteristics of both staphylococcal enterotoxin B and tularemia as effective biologic warfare agents we strongly recommend that the Department continue

with their development of vaccines and against the staph enterotoxin and to again talk with the Food and Drug Administration about potential licensure of the IND tularemia vaccine.

Fourth, given that Venezuelan equine encephalitis is both and endemic threat in certain areas of the world and a potential biologic warfare threat, again we recommend that the Department of Defense continue their advanced development of new VEE vaccine.

Fifth, we recommend that the Department pursue its initiated discussions with the Food and Drug Administration on issues regarding licensure of vaccines that have a potential significance as biologic warfare agents. Obviously the FDA doesn't see this as being a high priority for the population as a whole. It's a very restricted application. And we feel that the FDA needs to recognize this and act on this appropriately.

We suggested that perhaps a joint meeting between the AFEB and the Department of Defense with the Food and Drug Administration might be appropriate on this issue.

Among the potential topics for that joint

discussion would be a development of combination vaccine products of the type that we've been -- that I've mentioned here as well as investigation of facilitated immunization schedules to assure the ability to provide troops at potential risks with immunization on a rapid basis once decisions are made for deployment.

An important part of that obviously also is the need for the Food and Drug Administration to accept surrogate marker data for the potential effectiveness of vaccines against the biologic warfare agents since actual exposure situations are going to be very difficult to get accurate adequate data for protection.

And finally, looking to the future since vaccines are not effective or available against many of the potential biologic warfare agents we recommended that the Department devote adequate resources to studying and developing plans for the rapid deployment of troops to high-risk areas and determining what types of preventive measures or chemoprophylaxis might be appropriate. And certainly the AFEB would be involved in those discussions, but we felt that a lot of background

work needed to be done first.

DR. FLETCHER: Thank you, Jim.

Comments? Dr. LaRosa?

DR. LaROSA: I have a question actually problem for some of the epidemiologists here which is that when the IUM committee on evaluating the CCEP response to the Gulf War asked about information on experimental vaccine exposures among veterans we were told that there were no medical records kept of any investigational vaccines given. That there was rapid deployments and lots of people were immunized and it was not put in their medical records and it was not put anyplace where you could attach it to an individual person.

Beyond that, we were also told that because they ran out at certain circumstances -- in certain instances and didn't want people to think they weren't being protected they actually used placebos. So that self-reported receipt of vaccine is not accurate and that the physicians in many instances may not have known which was which.

Now, I -- I don't know if that's been corrected, if in all future deployments it's very clearly stated someplace that there will be medical

records kept of who gets what vaccine. But it seems to me that that's a good place to start, you know, to keep records, at least of who gets what.

DR. ALLEN: I'm not going to make a formal response except to say that I would certainly agree with you on that. I was not aware of that information. I haven't, you know, I hadn't heard that testimony or read that. And certainly to the extent that some of the vaccines used were investigational, there was supposed to have been an appropriate level of informed consent. And I'm surprised that there are not, you know, documented records of who it was administered to. It certainly should have been that way, I would think.

COL FOGELMAN: I think we -- Dr. Pittman, would you like to comment?

DR. PITTMAN: Sure, I would like to comment.

There was first, you know, a placebo that was being used. I have never heard that before in the Gulf War.

But let me give you another instance in which we did use an IND vaccine and that was to vaccinate troops in Bosnia. And there we vaccinated

over 3900 and we do have medical records including consent forms and other documents. And those documents are stored at USAMRIID. That was a very successful program and I think that will serve as a model for future kinds of deployments in which investigational vaccines or drugs might be necessary.

DR. LaROSA: So there's a procedure now that's been in place at least since Bosnia to handle that?

DR. PITTMAN: Absolutely.

DR. LaROSA: Okay. All right.

COL FOGELMAN: Dr. Connor?

DR. BARRETT-CONNOR: Could you expand a little bit on the surrogate marker question? Are you talking about antibody or animal studies or both or --

DR. ALLEN: Antibody response would certainly be the most direct of the surrogate markers available without, you know, having to have actual data on exposures and proof of vaccine efficacy in terms of disease prevention.

Yeah. I mean, antibody data clearly is the primary, you know, it's the primary method.

Certainly animal studies, if you've got a vaccine or an animal model and evidence that the vaccine provides proof against animals that have been exposed, that would be helpful also. Both, but certainly antibody primarily.

I've got just a point just to add about the --

DR. FLETCHER: Microphone.

DR. FRANZ: Our problem, of course, right now is licensure of these vaccines and we can't do phase three clinical trials with anthrax or with or with BOD or with plague by inhalation and so we have to use animal models for efficacy studies and in order to do that we need a surrogate marker. We can -- we can immunize you and we can immunize the animal. We can challenge the animal and measure something in that animal. And it's not always antibodies. Unfortunately antibodies just don't always work for all of these agents as markers of protection against inhalation challenge.

DR. BARRETT-CONNOR: That's part of why I was asking it.

DR. FRANZ: Yeah, looking for a lot of different things. With BOT for example, antibody is

good enough. It's perfect, it works just fine. But with anthrax we're having a great deal of difficulty right now finding a surrogate marker for protection.

We can immunize a rhesus monkey, twice, two weeks apart, wait, and he had a good antibody response. Wait two years, there's no measurable antibody, challenge him and he's still protected. So, it's those kinds of issues that we're dealing with.

DR. BARRETT-CONNER: Yeah, I was worried about the other way around.

DR. FRANZ: Right. Yeah. The other way around doesn't work either with anthrax. Just because he has antibody doesn't necessarily work if that antibody was administered passively. But if he was immunized and he has antibody it works. So it's not real clean. That's what we're looking for.

COL FOGELMAN: For the record that was Dr. Franz, Commander of USAMRIID.

DR. FLETCHER: Okay.

CAPT CUNNION: Captain Cunnion. Just for the record the order -- there was an order to record the vaccines. The Pendleton Marines did record them and DUMED does have those records -- during the

Persian Gulf.

DR. FLETCHER: Other comments?

(No response.)

DR. FLETCHER: Thanks, Dr. Allen.

COL FOGELMAN: Okay. Our next two speakers actually are Professor Sue Baker and Colonel Bruce Jones who are going to talk a little bit about visits to the Air Force Safety Center and just a tad about the injury report which you should have on your desk.

Bruce you need to use the microphone up there.

COL JONES: Okay.

COL FOGELMAN: There should be a walk-around mic.

DR. ALLEN: I think the walk-around mic is probably on the table.

(Asides regarding the microphone.)

COL FOGELMAN: Sue, if you want to speak, you might want to take the mic that's right behind you.

PROF BAKER: Okay.

COL JONES: What I thought I would do is I put together some viewgraphs. I think it will be a

little easier to track this.

But before I get into the viewgraphs, I thought I would tell you that the -- that the injuries in the military report is now out. I believe it has gone forward to health affairs, although I'm not sure of that.

COL FOGELMAN: They haven't seen it yet.

COL JONES: They haven't seen it yet.

COL FOGELMAN: Next week.

COL JONES: Okay. There are a few things that are different about this. One you'll notice there is a date on the cover now, November 1996. It's taken us a while to get to this point. What's new about this versus the other reports that you have is primarily that there is a foreword. It was written by Dr. Lou Kuller from Pittsburgh who is former chairman and also Dr. Barbara Hanson who was the co-chair of the injury work group and also the chapter written by the Board which was edited by Dr. Perrotta. It also has been revised.

And with those exceptions this is the same report that you've seen before. And we're pleased with it and I think that it's very timely. There's a great deal of interest in injuries, and I think

also it was apropos to our visit to the safety center.

What I'd like to do is just quickly outline for you what happened with that.

(Slide shown.)

COL JONES: A team of us was put together, organized by Colonel Fogelman and Major Bruce Koppley from OFSA in the Air Force at the request of the Assistant -- the Deputy Assistant Secretary of the Air Force for Environment, Safety, and Occupational Health. And the safety centers themselves were interested in proving their databases.

I must say that this was -- I think we -- we provided them with some helpful information, but also this was a very good learning experience because one of the things that it emphasized in my mind is something that I had read about and that is that you have to understand the purpose of a database when you try and begin using it for something other than its intended purpose. These databases maintained by Air Force Safety Center in particular but also the other services have historically been aviation based and migrated to a

broader purpose of looking at ground safety, but also especially at the Air Force this is an administrative event-tracking database.

And so what we got to see on the team was what happens when you take a very detailed data base that has an administrative purpose and try and use it for epidemiologic purposes.

(Slide shown.)

COL JONES: The purposes are as you see here, to consult with the Air Force Safety Center on their databases and the capabilities of those automated databases and also to acquire a better understanding of the process by which they acquire their ground mishap and other data and enter it into their computer system. And finally to make recommendations on means of enhancing the epidemiologic capabilities of those databases.

(Slide shown.)

COL JONES: The team was composed of Professor Sue Baker who is now a member of the Board, myself, Colonel Fogelman, Lieutenant Colonel Paul Amaroso from the Army Research Institute of Environmental Medicine, and Major Bruce Coppley from OFSA.

(Slide shown.)

COL JONES: The consultation was conducted in two phases. The first phase we received presentations and demonstrations on the mishap data systems maintained by the Air Force Safety Center and that was on July 7th through 9th. And then we had a review of some of that information that we saw previously and also a review of ground safety mishap data collection and reporting. And that was on the 14th to the 17th of October out at Kirtland Air Force Base in New Mexico.

(Slide shown.)

COL JONES: There are six or seven databases maintained by the Safety Center but the ones you see here are their main ones. The flight mishap database looks at aviation mishaps. The ground safety database looks at everything other than flight with the exception of things like space, explosives and missiles. And then there's a life sciences and human factors database which looks at ergonomic physiologic factors and mechanical factors that contribute to minor events, not terribly expensive, but mostly oriented towards flight.

And as I said earlier, it's important to

keep in mind that these databases serve a largely administrative function of have in the past.

(Slide shown.)

COL JONES: What we looked at in the ground safety center was how did they collect data. There were multiple sources of data including ER logs, hospitalization records, and several accident reporting forms, at least three or four different forms. And the process of validating those medical -- those forms and also the organization to which both military and civilian personnel belonged was very, very labor intensive.

The data entry process used the same degree of detail for Class A events which are deaths and serious injuries and events that cost more than a million dollars either because of damage to equipment or facilities and so forth.

The same level of detail for Class A as Class C which are mild to moderate events and costs less than $100,000.

The data entry process took many screens. I didn't count the screens of data entry, but there were, you know, probably 20 to 30. It was very labor intensive. And, again, the same degree of

information -- the same level of information required for all degrees of severity.

The other thing that we noted that we thought was important was there was limited feedback from the central data source to the individuals and organizations entering the data.

(Slide shown.)

COL JONES: These are recommendations that came out of the phase one review of the databases and we felt that they could enhance the functionality of that database if they identified it administrative versus epidemiologic needs and objectives. We felt it was very important that they linked their safety databases with personnel data, population data from the Air Force which they don't currently do. The Army has been doing that for aggregate data for a while, but not on an individual level.

The safety centers have not historically tracked rates and trends. The Army started reporting that and I believe the other services have started doing it as well, but it's not something that they have done historically. That's just started recently in the mid-nineties.

I think it's important to emphasize the strength of these databases is the detailed information on the causes of -- of mishaps and injuries and that that's something that they need to continue to do. We suggested that they use the international collaborative effort on injury statistics guidelines as a foundation for deciding what the core of those databases should be if they want to use them for epidemiologic purposes.

We also suggested that in addition to linking with the personnel databases and starting to calculate rates and trends routinely that they also obtain data from -- on injuries from hospitalization, disability, fatality, and out-patient databases. The latter, out-patient when it's available. That they should review rates and trends of causes of injuries in their databases and use those other databases to complement their own.

We suggested that they get a copy of the report that you just got. And also that the International Collaborative Effort, ICE on Injury statistics.

We recommended that they include an epidemiologist on their staff and by the second time

we were there they were in the process of hiring an epidemiologist. And we made a recommendation that they provide feedback to the field.

(Slide shown.)

COL JONES: On the second phase, we focused on ground safety, on Class C events because we perceived that that was the area of greatest weakness in these databases. They do a very good job of tracking and tabulating fatal and more serious mishap events, but the Class C which are far more numerous are clearly under reported for all three services and the Air Force is no exception.

And we felt that major problems were case identification, definitions of other types, access to medical records, the amount of paperwork involved, data entry time, all of which posed a huge burden on the safety personnel and kept them from doing other things that might be equally as productive.

We thought that they needed to begin looking and prioritizing where they focus their activities based on the frequency and severity. Actually that should be incidents and severity and costs of various hazards that they could also use

their databases for tracking and merging problems that they haven't seen before and that they could use it also to monitor the effectiveness of programs. None of those things are really routinely done at this time. And also again we recommended at this visit that they use other databases.

Clearly once we have outpatients' databases there's not a need to look at those minor injuries quite so much and that they should capitalize on the availability of hospitalization databases right now.

For Class C events we strongly recommended that they modify and simplify their data collection forms that they look towards using a minimum basic data set and they could get guidance from the ICE again for that. That they look at the AFEB report and that simplifying those forms would enhance the completeness of reporting among other things and would allow ground safety personnel to do other things such as investigations in safety programs rather than trying to track down data.

(Slide shown.)

COL JONES: Now, along with that recommendation we began working at their request on

a form that you see here. Dr. Sue Baker put this together and this is a preliminary form, but I think it's a very nice one that covers a lot of the material that the safety center would like to have and needs to have and it also -- it comes --

(Slide shown.)

COL JONES: -- it can be printed on the front and back -- on the front and back of one sheet. And I think that this is the sort of thing that one needs when you have numerous events to report. It's something very simple that captures the really critical information.

Sue do you care to provide comment?

PROF BAKER: What we were trying to do since the majority of Class C mishaps were not being captured by the database even the majority of hospitalized admissions for injuries didn't seem to be in any database was to create something that was simple enough that it could be filled out in a few minutes. Because the amount of time that was being spent by safety personnel trying to track down information, paper chases and so on, they felt -- I mean, it obviously was keeping them from doing their main job which was to prevent other injuries. So we

were pleased when they asked us if we could develop some sort of a simple form for them which hopefully would be -- see a lot more widespread use.

The idea here, down at the bottom that says in print too small to read, was that from the -- once with the name and social security number up at the top, from that one could get a bunch of information that would not have to be filled in, the person's age, and sex, and rank, and base, and that sort of thing. So the objective here was to get the minimum essential data on injuries, most of it in a checklist form, but with some words provided so one could then do word searches for things that we would never have coded.

And then on the back of this to go into detail for any single problem that -- I mean, if it was a motor vehicle incident there would be ten questions perhaps that could be answered with regard to that.

COL JONES: I can provide you with a copy of the briefing, Colonel Fogelman, and also a copy of the form here.

(Slide shown.)

COL JONES: I think, again, one of the

things in conclusion that just strikes me is that you have to keep in mind the intended purposes of these databases. These are really -- especially for the more serious aviation events -- databases that are administrative and archival in nature and allow you to track in great detail what happened for a specific event. And that's what they're intended to do. To know, was there an investigation done? What was the result of that investigation? And these are massive text fields. I mean, very cumbersome for use in epidemiology.

What were the recommendations of that investigation? Were the recommendations implemented and followed and so forth? And so it was a good learning experience and I think that with some simple forms such as Sue has recommended to them here and careful thought as to how they want to code these things that they have the potential for having a very potent database to help us understand the causation of crashes and unintentional injuries.

That concludes my comments.

COL FOGELMAN: Thank you. Can we have the lights please.

DR. FLETCHER: Thank you, Sue and Bruce.

Any questions or comments? Judith?

DR. LaROSA: First of all I commend you on what is -- I have not read it obviously yet, but an enormous piece of work and a very important piece of work. I think this as you have so nicely said on the front, a hidden epidemic, is very important. I've actually talked with Dr. Kuller about it.

One of my questions really because it goes to some information I had from the Institute of Medicine's defense women's health research issues is there are some data that I see you have in here regarding male/female differences. But I don't see a lot of data. Now, again, I haven't read it, so I don't really know. Were you able to collect is and is there anything that you wish to comment on that? Because I know musculoskeletal injuries are an enormous problem, or at least I have been led to believe they're an enormous problem for women in the military in large part or in some part because a lot of the equipment and -- well, a lot of the equipment have been designed for men?

PROF BAKER: The DOD has funded a study at Hopkins on injuries to women in the military. And we will be looking at a lot of these issues. Bruce

Jones himself has done a lot as far as training injuries to women and we spent time -- I was just out at the Air Force -- at Brooks and at their basic training center at Lackland Air Force Base. And had a very interesting time talking to physicians there and also seeing the basic training program getting some insight into the problems that can be created. For example, women in the security police who if, you know, a small-bodied woman having to carry an 80-pound pack uphill is probably going to have more trouble than your 50th percentile male will have.

But I think in terms of both the appropriateness of equipment there are both problems and opportunities.

Bruce, you may want to comment in terms of women's fitness in relation to what you found out about injury rates?

COL JONES: Yeah, I think this is an area that needs much more exploration. I've looked at injury rates among women in basic training and not only our own studies, but most of the studies throughout the '80s and early '90s have pretty consistently shown injury rates for women in basic training one and a half to two times higher than

those for men. But what we have found, at least in the Army studies, is that when you control for physical fitness there's not difference.

So, in other words, if you have men and women who can run the same times and do the same number of pushups and so forth that they have the same injury risks which suggests that the real underlying difference isn't physical fitness. And if you have men and women that have physical attributes that are similar, you can expect them to have the same injury rates.

In hospitalizations I think we need to look at it more after basic training the rates of injuries among women go down, but it may be because they're in different types of jobs than men after the basic training phase.

And, Sue, the Hopkins study I think should shed a lot of light on that because it's not only going to look at hospitalizations, but also disabilities, deaths, I believe, and safety data.

DR. FLETCHER: Dr. Allen?

DR. ALLEN: Can we get copies of the proposed data collection form?

PROF BAKER: Sure. We can make copies.

COL JONES: Yes, I'll provide that to Colonel Fogelman to get copies.

COL FOGELMAN: Sure.

DR. FLETCHER: Other questions, comments? Sue? Bruce?

(No response.)

COL JONES: Thank you.

DR. FLETCHER: Thank you very much. We'll move on.

COL FOGELMAN: Thank you. We have one more report today from Dr. Gwaltney who is going to talk a little bit about the acute respiratory disease surveillance meeting that we had in San Antonio a few weeks ago. Dr. Gwaltney?

Could you give him the microphone, please?

I want to thank -- while we're waiting -- both Dr. Jones and Professor Baker for helping us evaluate the Safety Center database. That's really going to help the Air Force in the future project how we need to improve that database. Appreciate it.

DR. GWALTNEY: Okay. Adenovirus I think as most of you know causes ARD which is a specific respiratory condition. And it is among the most, if

not the most important health problem of military recruits in basic training.

Before vaccine use up to 80 percent of recruits at some post developed ARD and up to 20 percent of these were hospitalized.

Also, up to 10 percent of those who sought medical attention for ARD had pneumonia on X-ray and while -- and severe and even fatal adenovirus pneumonias, although not common, are certainly well documented.

The illness rate typically peaked early in the second or third week of training just about the time the recruit became settled into the basic training routine they'd get sick, often get recycled and have to start over again.

Most cases were due to adenovirus types four and seven. Although other types particularly three and 21 were sometimes implicated. But when the vaccine was used these other types did not emerge as important causes of large epidemics.

In the 1960s Dr. Robert Channuk working with members of the armed forces developed an orally administered live vaccine for adenoviruses type four and seven. Separate pills were made for each of the

adenovirus types. This vaccine has turned out to be extremely effective and safe, is fully licensed by the FDA.

The vaccine was manufactured by Wyeth Laboratories as its sole source and has been routinely given at U.S. basic training posts since 1971.

First it was given only during the winter period, but because there were early fall and late spring epidemics of adenovirus in more recent years or since 1983 it's been given throughout the year.

Now, the adenovirus vaccine program when it's been combined with annual influenza vaccination and with bicillin prophylaxis for streptoccal infections when that's needed has controlled and essentially eliminated the problem of ARD in U.S. military recruits. And I think you've seen figures that have been shown to this group in previous meetings that show that. The recruits still have colds, but they don't have the disabling kind of infections associated with adenovirus.

In the mid-1980s the adenovirus vaccine program was discontinued at Lackland Air Force Base with no adverse effects and this probably resulted

from the fact that Air Force recruits have never had a major problem with adenovirus epidemics.

The current problem and the reason for the meeting in San Antonio which took place in November is that Wyeth has discontinued the production of the vaccine. In fact, they've dismantled the facility in which the vaccine was made. And at this time there is no other source and no future source of this vaccine which is available.

The current vaccine supply will be exhausted as well as outdated. Both of these things will occur about the same time in December 1998.

There's no good reason to believe that the ARD problem will not return to recruit populations once the vaccination is discontinued. There's been a recent study that shows that the serologic status of recruits has not changed but a high proportion of recruits is still susceptible to these two sera types of adenovirus.

Negotiations are underway with another vaccine manufacturer, but they appear to be moving fairly slowly. And even if successful it's unlikely that new vaccine will be available for several years.

The meeting in San Antonio was a tri-service meeting -- a group which addressed the problem of adenovirus ARD. It was chaired by Colonel Robert DeFraites of the Army Surgeon General's office who is here. And it addressed three major concerns, three subgroups met to discuss these problems.

One group looked at surveillance of ARD in recruits under baseline and outbreak conditions. And the subject which were included in this discussion were case definitions, methods of surveillance and reporting, and establishing of action thresholds.

A second group looked at the laboratory diagnoses of ARD including the availability of facilities, personnel, and reagents. The turnaround time for diagnosis in outbreak situations and identification of sera types four and seven sense if outbreaks occurred due to only one of these types it might be possible to conserve the vaccine supplies if this were known.

And then the third group looked at disease control what epidemic response should be made in the late spring, summer, and early fall when it's now

planned that vaccine will no longer be given during those periods. It won't be given on a year-around basis in order to make the supplies last longer.

How to use the vaccine currently available and how to ensure rapid access to bases that need it. And then finally the contingency plans when the vaccine is no longer available and these included the old things that had been tried in the past such as ventilation, improved engineering solutions, handwashing, spacing, head-to-foot sleeping in the barracks, things that have never really shown that they worked particularly well, or which are impractical in terms of redesigning large numbers of barracks and buildings. The details of these recommendations are available for those who are interested.

The problem of finding a new vaccine supplier was discussed. It was recognized this is beyond the control of preventive medicine commands. This is really the responsibility of contracting and purchasing commands and it is ultimately the responsibility of the line commands.

The case for continuing the vaccine program seems very persuasive and I think many of you have

seen the review by Colonel Joel Gatos and his wife Dr. Charlotte Gatos. They estimated the cost of one in-patient episode of ARD, that is a three-day hospitalization, and the training cost is approximately $3,000.

The cost of one immunization in recent years has been a dollar and 35 cents. The manufacturer contended that this price was too low and one of the problems in the negotiations, I guess, was the cost they were going to charge. A figure of $10 a dose is one that has been mentioned. I don't know if that's a realistic cost or not.

Approximately 200 to 250 doses of vaccine are needed per year to immunize the target populations of recruits. Dr. Gatos did a benefit/cost ratio which came out to be three or four fold. And, of course, there the additional costs and the morale disorganization --

DR. POLLAND: Jay, excuse me. Could you say again how many does are needed?

DR. GWALTNEY: Two hundred thousand to 250,000. Up to a quarter of a million doses. That actually is not a very large gross if you are charging $10 a dose, they use 2.5 million, I

wouldn't mind making that myself, but I gather that that's maybe peanuts for some drug companies and that may be part of the problem. To start up a new facility to put in GMP, good manufacturing practice, and so forth would cost more than that certainly to begin.

DR. POLLAND: Are there any other military units around the world or are there any other consumers of this vaccine, or is it just a vaccine for the U.S. Department of Defense?

DR. GWALTNEY: I think it's only the United States Armed Service.

COL FOGELMAN: Are you aware of any other consumers of the vaccine, Bob? Any other consumers of adenovirus vaccine besides the military?

DR. DeFRAITES: The adenovirus four and seven is licensed for military use only in the United States. There are -- there are no other, to my knowledge, any other military consumers. The Canadian forces at times in the past have used the vaccine. I don't think they are using it now. At least when I checked in mid-summer they weren't that -- they weren't using it in their recruits. They had very few recruits. I think there is

representative from Canadian defense force here today maybe who can address that.

In Europe my understanding was that there was use of an adenovirus vaccine by one or more of the European forces years ago, but I am not aware that -- and Wyeth had no other customers other than U.S. military.

DR. GWALTNEY: Another part of that is that in other -- In the United States the population side -- recruit population size is much larger than most other countries. And that seems to have some effect on the size of the epidemics. And so the problems in other countries apparently have not been as large as they have in these -- in our large recruit training posts in the United States.

DR. CLEMENTS: I just want to ask a question that because they have built -- Wyeth has built new facilities that could be used for that purposes, but is it the reestablishment of the GNP and meeting all the criteria for the FDA that's the problem or is this --

DR. GWALTNEY: I don't know the answer. Maybe Colonel DeFraites does. I'll just say one more thing and then I'll finish. The AFEB has been

aware of this problem for over two years. We made a recommendation on February the 28th, 1995 that adenovirus vaccine acquisition be given, quotes, "the highest priority" and quotes "pursued vigorously." This apparently has not occurred quite as well as we would have liked it to happen. And I think it is unfortunate that this vaccine is not going to be available for our recruits. Not only because of the fact we are disrupting -- we will have major disruptions in training, but we have people who are not getting things that would help them from getting sick. I think that's really the bottom line.

(Cross-talk.)

DR. GWALTNEY: I think maybe other people here in the room could comment on that better than I can.

COL FOGELMAN: Bob, I think you need to --

DR. DeFRAITES: What was the question?

COL FOGELMAN: Come up to the mic, please.

DR. FLETCHER: Is it a monetary problem only?

THE COURT REPORTER: Excuse me. Could I

have you all identify yourselves when you speak. I do not know who is speaking.

COL FOGELMAN: Okay. Sure.

DR. DeFRAITES: I didn't hear what you said.

(Laughter.)

COL FOGELMAN: Okay. Just speak up and if you have a question please come to the microphone.

DR. DeFRAITES: This is Lieutenant Colonel DeFraites, I didn't hear what was said.

This is Bob DeFraites. In response to the question about Wyeth's decision not to continue the manufacture. As far as we understand -- well, there's been a lot of corporate changes at Wyeth and I think they are owned by American Home Products and as I understand it's a business decision not to pursue the vaccine any longer.

Wyeth, though, has been sending -- has been concerned about continuing this facility for about ten years and finally they decided to not continue manufacture anymore. And there's a lot more to it that I really can't go into here.

DR. FLETCHER: Any questions or comments for Dr. Gwaltney or Dr. DeFraites?

(No response.)

DR. FLETCHER: Okay.

DR. GWALTNEY: Well, I just think the Board again should do all we can to help because I think it is a serious problem. We've talked about a number of things this morning which I don't want to minimize. But in terms of morbidity and impact on military preparedness I think that this is -- this ranks very high on the list of problems that we're addressing.

DR. DeFRAITES: I did want to make one more comment. This is Lieutenant Colonel DeFraites again.

I think the thing that we're concerned mostly about on the surveillance side is what assets DOD might have at their disposal to evaluate especially on the laboratory side, the laboratory aspects of acute respiratory diseases and recruit populations. A lot of our capabilities have deteriorated over the years and are now faced with an old threat that had long since been taken care of and assumed not to be a threat by use of this very effective vaccine now is once again raising its head. And one of things we're wrestling with in

this surveillance, ad hoc working group that we've been -- that I -- that we've been meeting with the last several months has been what should be our response and how can we assure that we still have capability to deal with adnoviruses in the recruits.

Part of that is addressed for the time being. There is at least one research protocol that Dr. Gray is here he may can give details if people are interested of collecting adenovirus sera types that might be circulating at basic training posts. And that the purpose -- one of the purposes of that would be to validate that these sera types number four and seven are still the threats that we think they might be. And along with that is going to be on the clinical side to ascertain incidents of -- of ARD and what proportion of these ARDs are comprised by adenovirus.

DR. SOKAS: Is this a disease that would be considered for antiviral treatment if there is no vaccine to prevent it, or is there anything available?

DR. GWALTNEY: No, I don't think there are any antiviral that work well for adenovirus. Certainly none that are close to being useful

clinically.

CAPT GRAY: This is Greg Gray from the Naval Health Research Center. Thanks to Pat Kelley's recent book we've just had an intensive review of this and there were some success stories with respect to serum and englobulin as a prophylactic agent as an alternative. It certainly wasn't as good as the live vaccine, but it seemed to have some efficacy.

DR. FLETCHER: Dr. Allen?

DR. ALLEN: I'll make two comments. One on that -- on the treatment. Obviously if you can prevent you're much better off. It's much less expensive. It's much easier to apply.

The other point I was going to make about the vaccine availability is that it's distressing that this is the kind of business decision that is being made when obviously it has a real impact. Potentially could have some utility, I think, in the civilian sector, but obviously it hasn't been used that way. But as we are looking at the development of other vaccines or which predominantly will be for the military population only. I think we're going to have to address the issue of -- of production and

availability on a continuing basis.

DR. FLETCHER: Dr. Chin?

DR CHIN: I don't know if there's anybody from the Air Force here, but my understanding is that the Air Force no longer uses it and I think that one of the primary reasons that they don't have recruits diseases at their quarters. Is it true that, you know, the Air Force it's four to a room?

COL FOGELMAN: No. Not in basic training.

DR CHIN: Not in basic training?

COL FOGELMAN: No. No, it's not.

DR CHIN: But yet they're not using it. And they're not having the problems. It's the size of their --

CAPT GRAY: One of the differences -- this is Greg Gray, Naval Health Research Center. One of the differences in the recruit training is the duration. The Air Force trains for six weeks. The Army and Navy, I believe, for eight weeks. The Marine Corps for 11 weeks plus additional close-quarters training. So based on the -- those durations we have different proportions that are sequestered or in close contact for -- and get a higher attack rates.

COL FOGELMAN: There are a number --

DR. FLETCHER: More questions?

COL FOGELMAN: -- I think there are a number of other factors involved in this.

DR. FLETCHER: Dr. Polland?

DR. POLLAND: Ask out of ignorance, but isn't it the case that some products that might be considered orphan products can get some kind of monies from the Federal Government in terms of their production and distribution?

PARTICIPANT: Drugs, but not vaccines.

COL FOGELMAN: I don't know. Anybody in the research community --

I don't know the answer to that.

PARTICIPANT: No vaccine. Otherwise we'd be doing something great.

DR. STEVENS: I had a related thought to that. You were referring at the beginning to the contract and you said maybe it's a contracting issue. The military is certainly contracting for lots of vaccines and it seems to me that what you want to do, if indeed this is worthwhile, and I don't know, I don't have any way of judging that, but if this is worthwhile you want to throw it into

the contracting mechanism and then make it a package because they've got a lot of buying power on the side of the military and they could get somebody to produce it if they wanted to.

Then the next question is, is it worth the price you're going to have to pay for it? And that's not clear from what you said. If Wyeth is going to require 10 bucks for a dose and you say the cost benefit is three to one or something, or four to one, then it's not obvious.

DR. GWALTNEY: I should have made that clear. I think he calculated the cost benefit on the ten-dollar cost of the dose, not on the --

DR. STEVENS: Oh, on the ten-dollar?

DR. GWALTNEY: Yeah. Yeah.

DR. STEVENS: Well, then why won't they pay it?

DR. GWALTNEY: Well, again, I don't know. I do know that another manufacturer is in negotiations and they may make it. If they do there will be this period of time when the vaccine is not available. How long it will take for those negotiations to be completed, if they are completed, I don't know. And I really have not been involved

with that part of it at all. I just learned this at the meeting. So, again, there are people here that I'm sure know more about it than I do.

COL FOGELMAN: Dr. Nang?

DR. NANG: Yes, this is Major Nang. I'm with the U.S. Army Center for Health Promotion and Preventive Medicine. I actually did the cost benefit analysis with Colonel Gatos and the cost benefit analysis does take into account the higher costs of the vaccine including potentially a surcharge to be imposed by DPSC which is Defense Personal Support Center.

So it's a very effective vaccine as this gentleman pointed out. And unfortunately we're still unable to -- we've got one company that's interested and Colonel DeFraites has been working with Health Affairs to work on the contract.

A few other -- a few other points of clarification. In terms of the licensing for use of the product it is for military recruits as Colonel DeFraites did point out. But it is helpful to keep in mind that within the past year there has been an outbreak of adenovirus that occurred in the State of Louisiana. It occurred in a children's long-term

nursing care facility. And this was a significant outbreak in that for the most part historically we have not seen deaths associated with adenovirus infections, but in this case at least eight of the children died.

Those are some potential expan -- that's a potential new market there if that's a possibility. I've been -- we've been soliciting pharmaceutical companies and an RFP did go out to all the major manufacturers with only one company that was interested.

COL FOGELMAN: What type of adenovirus was that?

DR. NANG: I believe it was an adenovirus four.

COL FOGELMAN: Four? Okay.

DR. NANG: I may be mistaken.

COL FOGELMAN: Other questions?

DR. FLETCHER: Other comments?

COL FOGELMAN: Comments?

(No response.)

COL FOGELMAN: Well, I think this is an issue if the infectious disease control committee wants to take this up later in committee session, I

think if you have some suggestions for ways to help us, we'd appreciate it.

DR. FLETCHER: They may have a committee report of some response tomorrow.

COL FOGELMAN: Colonel Kelley, are you here? Yes. Okay.

Now we're going to have a few more briefings before we break into committee session. First we're going to have Lieutenant Colonel Pat Kelley who is the Director of Preventive Medicine Department at Wrair talk to us about the DOD accession medical standards analysis and research activity which is just starting.

(Pause.)

LTC KELLEY: May I have the first slide, please?

(Slide shown.)

LTC KELLEY: Thank you very much, Colonel Fogelman. Good afternoon, members of the Board. It's certainly a pleasure to be here this afternoon and to brief you on a major new epidemiological activity recently established here at the Walter Reed Army Institute of Research.

It will be dealing with accession policy

issues. Issues of this type have sometimes been brought before the board, but in most instances they have been debated in other circles. But I think these issues dovetail quite nicely with the capabilities and purpose of the Board especially now that efforts are underway to make the standards development process more evidence-based as opposed to the more clinical opinion-based approach that has historically been taken.

In mid-September after about two years of discussions, the accession medical standards analysis and research activity received initial startup funding. And we're off to a productive start and are confident that this activity will help put accession issues in the proper perspective, improve readiness and personal health and reduce wasteful and inefficient practices.

Next slide, please?

(Slide shown.)

LTC KELLEY: As we see it our mission is to support the development of evidence-based accession standards through first guiding necessary improvements in the medical and administrative databases underlying standards of valuation; two,

conducting epidemiologic analyses to provide military-specific insights into accession's issues; and three, to prepare policy recommendations that integrate relevant, operational, clinical and economic considerations.

Next slide, please?

(Slide shown.)

LTC KELLEY: Before delving into how AMSARA is progressing I would like to provide a brief overview of the enlisted accession and attrition process.

The primary applicant pool for military accessions are persons aged 18 to 24. In the United States there are approximately 25 to 30 million persons in this group. For every birth-year group recruiters need to successfully enlist about 11 percent of the men and about one percent of the women.

Now, more actually need to be recruited because some are disqualified either by the recruiter or as a result of the military entrance processing command evaluations.

In fiscal year 1996 MEPCOM did about 362,000 physical examinations to get approximately

250,000 accessions.

About 47,000 applicants were rejected permanently for a variety of conditions. There were about 6,000 applicants who were disqualified initially, but applied for waivers and received those waivers and thus could join the accession pool.

After being accepted for entry individuals spend anywhere from about a day to about a year in a delayed-entry program from which they can drop out prior to actually getting on board the bus to go to basic training.

May I have next slide, please?

(Slide shown.)

LTC KELLEY: As I said, and this is incorrect, this should be about 250,000. About 250,000 people arrive at basic training and as you can as they go through the process a number of them drop out. About 10 percent drop out between the reception center in basic training, another four percent drop out during advanced individual training. And then as you can see, during the first tour of duty another 20 percent drop out. So you have over -- or roughly 35 percent of the accessions

into the military do not complete the contractual term that they signed up for.

The sheer magnitude of this attrition coupled with further resources that are consumed on things like medical care and retraining, the sheer magnitude of this more than justifies a systematic evidence-based approach such as now underway with AMSARA and the accession medical standards working group.

The accession medical standards working group, by the way, is the group that we ultimately answer to. It's a group of about ten flag-level officers representing the medical and personnel sides of each of the services and of the Department of Defense. It's co-chaired by Dr. Mazuki [phonetic] who is the Deputy Assistant Secretary of Defense for Health Affairs who has been at these meetings many times before, and Lieutenant General Ebison [phonetic] who is the Assistant Secretary of Defense for Military Personnel Policy.

I'd like to point out that of these attritions during basic and AIT about 4 to 5 percent -- in fact, it's at least 4 to 5 percent are for conditions that existed prior to service. In some

cases, though, if these conditions are ultimately shown to have been known to the applicant but the applicant chose to deny it on his entry history exam form, the person is not discharged as an EPTS discharge, but rather as a fraudulent or erroneous discharge. And then some individuals are discharged for quote, "failure to meet performance criteria" which is sometimes a euphanism for not being adequately motivated.

(Laughter.)

LTC KELLEY: Next slide, please?

(Slide shown.)

LTC KELLEY: To summarize this issue, military entrance processing command applies current accession standards now in over 300,000 accession exams per year. For those who ultimately take the oath and enter DOD spends about $20,000 per enlistee to provide them their initial entry training.

About 25,000 enlistees per year wash out during initial training with about a third overall finishing -- failing to finish their first tour.

Considering the costs represented by these losses AMSARA is a minuscule investment. And the bottom line is thus, that ever time AMSARA

identifies the means to prevent 50 of these 25,000 attritions annually it pays for itself and this does not even include any savings from avoided medical care, sick leave or disability.

Next slide, please?

(Slide shown.)

LTC KELLEY: AMSARA has six primary objectives all aimed at institutionalizing evidence-based policies and procedures. Later I will go into the objectives in detail but for now I'd like to list them to orient you to where we intend to go with this project. The first objective is to validate current and proposed standards.

Given valid standards and then we need to determine whether the tools used for their assessment measure what we think they measure.

Third, AMSARA will support medical and administrative quality assurance assessments.

Fourth, it should help improve the accuracy of our assessment methods and determine which techniques are cost effective.

Fifth, as policies and procedures are changed and waiver is granted, it will be critical to systematically track measures such as attrition

and hospitalization.

Finally, AMSARA should proactively recommend changes to enhance readiness, protect health and save money.

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LTC KELLEY: To accomplish these objectives we have developed a structure that includes six government employees depicted by the greenish boxes and four contractors depicted by the black boxes. The contractors on this project will all be full time except for the health economist who will be devoting about a third of this time. The government employees including two preventive medicine physicians will spend a third to two-thirds of their time on the project.

The AMSARA is situated in the division of preventive medicine at WRAIR. WRAIR, as you probably know, features many scientific departments that are relevant to accession's standards/issues. And that was one of the reasons why it was chosen to put this here instead of other institutions. Not only do we have a significant epidemiological capability but with our divisions working with

respiratory research and clinical physiology, hematology, military psychiatry and behavioral biology we can coordinate many of the spin-off projects that are undoubtedly going to come from this.

When WRAIR is joined by the Navy Medical Research Institute at our new laboratory building under construction the integration of members of the other services into this endeavor and spin-off projects will be facilitated.

Next slide, please?

(Slide shown.)

LTC KELLEY: The success of this project depends very much on a coordinated effort by many committed collaborators. One of AMSARA's prime partners is the U.S. Army Center for Health Promotion and Preventive Medicines, Army Medical Surveillance System. This surveillance system grew out of the HIV surveillance system developed at WRAIR in 1985.

The Army Medical Surveillance System includes detailed demographic, aptitude testing, and medical exam data on recruit applicants for the Army, Navy, Marines and Air Force. And this data

goes back to late 1985, as I said.

The MEPCOM data archive serves as a very cost effective tree upon which to hang the other data necessary for this product. Along with the MEPCOM, other major data sources that play a key role are DODMERB which is the Department of Defense Medical Examination Review Board which handles officer accession exams. MEPCOM handles enlisted accession exams for the most part and most of the officers go through DODMERB.

DMDC, the tri-service waiver authorities and tri-service patient administration databases are also part of this.

We have begun discussions with a new resource in DOD for disability data which is the joint disability evaluation and tracking system or JDETS.

Next slide, please?

(Slide shown.)

LTC KELLEY: Much of the data we need is already in hand or access has been arranged. This includes MEPCOM files, enlisted gain and loss files, other archived DMDC personnel files on officers, tri-service hospitalization files and files created

at the MEPCOM on accessions who separated in the first six months of service with conditions that existed prior to service.

As I will elaborate on later, several of these files, while useful now have significant limitations because of the inadequate standardization of definitions and the use of diagnostic groupings that have little medical basis.

Data to be acquired is listed on the right and includes the officer exam data from DODMERB, data from other commissioning exams, disability data, waiver data, and casualty data.

Next slide, please?

(Slide shown.)

LTC KELLEY: Getting back to the objectives of AMSARA objective one is to validate current and proposed standards. Though I think we should base the issues we study on a prospective developed from the data rather than merely from what is politically hot at the moment. It is likely that the issues laid out on the left here will be prominent items on our agenda for the next year or two.

We will approach many of these questions using survival methods -- survival analysis methodologies. And example of a hypothetical survival analysis is shown on the right. In it persons with flat-foot waivers -- flat feet are considered a disqualifying condition at the moment -- persons with flat-foot waivers are compared with those who don't need such a waiver.

Obviously at accession 100 percent are survivors. That is on active duty and unscathed. A failure to survive can be represented by end points such as an EPTS discharge. A foot-related hospitalization or some other non-favorable outcome.

The very first survival analysis that we're going to be doing actually relates to asthma and I'll talk a little more about that in a few minutes.

Radial keratotomy and PRK are issues of major concern right now. Attention deficit disorder when I was growing up they didn't have such a label, so you could deny this when you came into the military, but now there are a number of children who are into military age who are carrying a label of ADD and we're trying to figure out what to do about that.

And then there's a question relating to syphilis which I'll go into in a moment.

Next slide?

(Slide shown.)

LTC KELLEY: The second objective is to validate techniques used to determine compliance with a standard and this is critical to do.

When I read the draft Government Accounting Office report on attrition I came to wonder whether the GAO had a good understanding of test performance issues and the potential impact of suboptimal tests on recruiters. The GAO report authors seemed to focus on increasing sensitivity because obviously they want to reduce the number of erroneous accessions. But as we all know it's not unusual when you increase sensitivity to decreased specificity and that will increase the number of erroneous disqualifications. And the recruiters are having enough trouble recruiting people as it is now without us labeling people who would do fine as inappropriate for accession.

Next slide, please?

(Slide shown.)

LTC KELLEY: Objective three is to monitor

medical and administrative quality assurance. One aspect of this is to track EPTS discharge diagnoses, which as I said are discharges that for conditions that existed prior to service.

This is essential if we are to understand attrition. It's becoming evident that much work needs to be done to standardize diagnostic codes and ensure that discharge diagnoses are specific enough to be useful. Currently different training centers and the different services characterize the same problem differently in some cases. And some of the diagnostic groupings as I noted are epidemiologically not very useful.

For example, in the MEPCOM physical exam all disqualifications for feet problems are lumped together and you can't determine whether the person has flat feet, high arches, missing toes, malformed toes, whatever.

Next slide, please?

(Slide shown.)

LTC KELLEY: Other quality assurance questions deal with monitoring the outcomes of waived accessions by the authority that granted the waiver. Waiver authorities come from a variety of

clinical backgrounds and have varying amounts of experience. The performance of waived individuals may vary some by waiver authority and this may suggest areas to improve the collective waiver granting process.

These are complex issues and would deserve a careful collaborative review before recommendations were made though.

Another type of quality assurance analysis would be to monitor geographic variation in diagnoses across MEPs centers. And I have some preliminary data to just illustrate this point.

Next slide, please?

(Slide shown.)

LTC KELLEY: The frequency of some conditions may vary between recruit applicants in different parts of the country. One would expect that for most conditions the frequency of ill health would not vary that much around the country. We looked at MEPS disqualification data from about five or six years ago so you can't blame the people who are sitting in those jobs now --

(Laughter.)

LTC KELLEY: -- and noted some wide

variations in the frequency of disqualifying conditions. For example, applicants seen at the Beckley, West Virginia MEPS were more than 10 times as likely as applicants from New York City to be disqualified for hearing deficits. Applicants from Spokane were about four times more likely than those from Fort Jackson to receive chest and lung disqualifications. And applicants from Denver were about 17 times more likely than those from Puerto Rico to receive upper extremity disqualifications.

Well, what can we learn from this? Well, it would be very interesting to compare EPTS discharges for people who came through different MEPS if they correlate inversely with disqualification rates we may be able to recommend improvements. If EPTS discharge rates have no correlation with widely divergent exam stations, then we may say something about the importance of the finding for predicting attrition or some other undesirable outcome.

Next slide, please?

(Slide shown.)

LTC KELLEY: AMSARAs objective four is to optimize assessment techniques to ensure that we

take advantage of improvements in technology or capability or other logistic elements. One such example that we're working on is the question of whether we should continue syphilis screening at MEPS. The issue is particularly sensitive in recent years because under the Clinical Laboratory Improvement Act the MEPS stations must now employ for the sole purpose of this test a more costly certified laboratory technician.

In the past this level of training and certification was not required. We're now exploring five options which you see here which range from the status quo through screening only higher-risk groups such as those from high-risk geographic locations to trying to drive the cost down by tacking the syphilis screening onto the HIV contract, and having the testing done centrally, to having the syphilis testing done only after the applicant gets to basic training. Since syphilis is almost always treatable and this could probably be done in such a way that you didn't have to send the positive candidate out to get his test on the -- his FTA-Abs and treatment on the local economy and then potentially lose him from coming back into the pool.

And we could also potentially drop testing altogether if the disease is considered rare enough and the consequences are not relevant to the purpose of the examination.

Next slide, please?

(Slide shown.)

LTC KELLEY: So far in our analysis which is just preliminary we've learned several things. First it cost MEPS over $7.00 to do an RPR syphilis test. As I said, this reflects the cost of having a technician on board just for that purpose.

Locally when an RPR screening test is positive it has to be -- the person has to be sent out for an FTA-Abs which runs about $10.00. We've been able to determine from the MEPS HIV testing contractor that they would be happy to do our RPR testing for only about $2.00 a test and do the few follow-up FTA-Abs tests required for $2.99 each. Thus, this contract mechanism could save as much as $1.6 million per year or at least free up those laboratory technicians at the 65 or so MEPS stations for other things.

Next slide, please?

(Slide shown.)

LTC KELLEY: Another aspect of optimizing assessment techniques that we hope to pursue is related to attrition. And as I noted attrition is a huge concern in various DOD circles these days stemming from the fact that the Congress asked the GAO to look into this question because they were very troubled by the fact that we lose about a third of our recruits before they finish their first contractual tour.

We hope to explore how well the DOD might be able to predict attrition based on data in the MEPCON file on areas including educational attainment, body mass index, medical exam findings, employment history, AFQT which are IQ tests sort of scores, and police record. Currently these things are part of the qualification process, but they're treated more in a univariant fashion rather than a multi-variant fashion. So hopefully we'll be able to develop a tool that may enable recruiters to more quantitatively assess whether the investment in training is likely to pay off.

Next slide, please?

(Slide shown.)

LTC KELLEY: The fifth objective of AMSARA

is to track the impact of changes in policy and procedures. This is a hypothetical example of what we might see if there was a change in the policy regarding asthma waivers. The current standard is that no person with a reliable history of asthma may access into the military. Though in the last several months the Navy has been granting blanket waivers if no symptoms or treatments have been noted since the age of 12.

The official standard, though, remains a total ban on present or former asthmatics even those who haven't had a symptom since, you know, the age of two or three.

Until a few years ago the official standard was no asthma symptoms or treatments since the age of 12, but after about 250 evacuations from DESSERT SHIELD and STORM General Schwartzkopf pushed to have an absolute standard and without a whole lot of evidence being brought to the question that's what we got.

In this hypothetical example which is just to show the type of thing we might be able to do, we can obviously look at rates for early discharges over time before and after the implementation of

policies.

And now the final objective.

Next slide, please?

(Slide shown.)

LTC KELLEY: And that is to recommend as we mine the various databases possible areas for change further analysis and specific research projects. With AMSARA based in a research oriented command we are well placed to help align our research priorities toward issues that are highly relevant to the accession and training communities whether it be better methods of data documentation and proved productive models, more accurate diagnostic tests, or more insightful psychological screening. And this just shows some of the possible changes that I have alluded to already in areas like data coding, shifting syphilis testing.

In fact, the decision was just made last year to recommend to the steering group that the pelvic exam be dropped from the MEPS stations. This does not -- in fact, you may think this reflects and insensitivity to female reproductive concerns, but, in fact, it's rather the opposite. And some of the strongest proponents were from the Women's Health

Group. And the reason for that is at the MEPS station these women, for a variety of reasons, were not getting PAP smears. Usually shortly after they got to basic training they were getting their PAP smears and the issue was that they were putting these women through two pelvic exams within a fairly short period of time and in many cases this was their first pelvic exam at the MEPS station and it was not felt that the sort of production line environment of the MEPS station was the best place to have one's first pelvic exam.

So, I can assure you that women coming into the military are getting pelvic -- are going to be getting pelvic exams with PAP smears, but it's not going to be in the production line setting of the MEPS station.

And they were comfortable with this because it was felt that very few women had untreatable conditions found on the pelvic exam and the primary purpose of the screening exam to get in the military is not to provide health care but rather to determine whether you should be qualified or disqualified.

Why don't we go on to the final slide and

I'll just show what some of our goals are for the next 12 months.

(Slide shown.)

LTC KELLEY: And one is to solidify our future active duty staffing. We need active duty people to guide and oversee our contractors. We need to prioritize the projects we work on so that they're not based entirely on whims of various interest groups and hopefully we'll be able to prioritize them based on evidence. We need to promote more specific data documentation and standardized data coding across the services and within the service.

Our first three deliverables are going to be the syphilis project, actually it will be a fourth deliverable. The syphilis analysis I alluded to before which should be out in the next few weeks. An annual descriptive report, basically the descriptive epidemiology of these items I've touched up.

We plan on doing a survival analysis looking at individuals who had in recent years have come in with asthma waivers, and then trying to develop a better model to predict attrition.

And that's the last slide, I'll be happy if there's time to --

COL FOGELMAN: Could we have the lights please.

LTC KELLEY: -- address any questions you might have.

DR. FLETCHER: Thank you very much. Are there questions?

(Applause.)

DR. FLETCHER: Dr. Baker?

PROF BAKER: I'm sympathetic with recruiters who are having trouble meeting their quotas, but I wonder whether -- I mean, there's no disincentive for the recruiters as far as getting in people who subsequently drop out. And I'm just wondering if when somebody drops out if that dropout shouldn't be sort of charged against the recruiter dropping it away from his quota of possibly -- you know, if one person drops out, subtract 1.2 from the number that he's met.

LTC KELLEY: That's a good point. And, in fact, my Navy colleagues can correct me if I'm wrong, but my understanding is in the Marines that's exactly how it's done. The Marine recruiters do not

get a credit for a recruit unless that recruit finishes basic training.

In the Army -- and I am not sure about -- I don't think anyone else does it, in the Army the philosophy behind not doing it was that they didn't want to penalize the recruiter if he was doing a good job, but the person washed out for some reasons unrelated to his job performance.

These recruiters are under tremendous pressure and they sort of saw it as a fairness issue in the Army.

DR. FLETCHER: Have a question? Please identify yourself each time because we're recording and we need identification.

Other questions.

(No response.)

LTC KELLEY: I'd just like to say I'm hoping that we can bring these questions of this type to the Board in the future. I found it almost astounding that most of the people involved with this process, the waiver authorities, the standards' gurus in the different services really didn't have a clue what the AFEB was all about. And, in fact, I'm going to be doing a lot of epidemiologic analyses

and most of them have very little epidemiologic background. And so I have been suggesting to them that just as a somewhat of a quality assurance check on me we have some of these issues vetted before people who understand evidence-based analyses and policy development.

COL FOGELMAN: Thank you very much.

DR. FLETCHER: Thank you very much.

(Applause.)

COL FOGELMAN: We're going to have one more speaker and then we'll take a break before our next speaker.

Our next speaker is Dr. James Helmkamp who recently -- in 1995 -- retired from the Navy after 25 years. His last Navy assignment was with the Division of Safety Research at NIOSH and he conducted research on occupational-related fatalities and active duty deaths. And he's going to talk to us today about some work he's done developing an active duty national mortality profile from 1980 to 1983 of which you're all going to get a copy today.

Dr. Helmkamp?

DR. HELMKAMP: Thank you. I would like to

provide a little bit of a background of how this document came to be, a little bit of the history of where I came from and then the utility and use of the information that's contained in this document.

I was assigned to the CDC in the National Institute for Occupational Safety and Health in 1991. And one of my major assignments was to develop a database that would contain information on the occupational injuries that could be compared with national databases by comparing DOD and national information.

The primary sources of this information were twofold. One was for fatality data which was based on the DD1300 which is filled out on all active duty members who die on active duty.

The population data that I used was derived or obtained from the Defense Manpower Data Center in Monterey, California. And, thus, we were able to calculate rates and identify risk groups. We were able to obtain this data from 1980 through various periods but most recently '80 through '93. And similarly with the population data.

I have previously presented with the Armed Forces Epidemiological Board several times on the

military fatality database. I think most recently, as I recall, in 1993. I've also presented results on various aspects of my research with the Navy Surgeon General's Office also with the Medical Officer of the Marine Corps.

Also data has been presented nationally -- excuse me -- nationally at the American Public Health Association Conferences, Navy Conferences, and other professional meetings. And also there have been about five or six publications and peer review literature relating to this information.

The document itself is 50 pages of summary of the mortality experience of active duty individuals who have died on active duty during the 14-year period, 1980 through 1993. The document itself is divided into three, four major -- five major sections. I'm sorry.

Those are: the summary for all services, looking at accidents, injuries, diseases, homicides, and suicides. And then for each individual service has similar information broken down demographically.

The intended use of this document is to provide a source document with long-term data, 14 years of data that can be used as a source book for

comparison with newer data that comes out for trend analysis and comparison purposes and also with national databases that exist.

We have brought about 150 additional copies that I would suggest that would go to the Surgeon General's Offices that could be distributed to preventive medicine and occupational health officers.

Also, I would suggest that some could be taken to the medical school for use.

The main source of information as I mentioned earlier was the DD1300. And this is a very useful document but I think it has several limitations. One of those is that it -- although it has an area where you can indicate on-duty or off-duty time of death. That is used at the option of each service. And each service now is -- it's not consistently used. Therefore, comparison with data that the National Institute for Occupational Safety has on work-related deaths is problematic. You just can't do it.

Another shortcoming is in the cause and circumstances section of the DD1300 that I think that could be expanded to allow a more narrative

description of the cause of death other than just a code of death with the ICD9 coder or 10. I think this could be designed simply and with the existing form as it is now. But that would provide you more information, particularly when you get into types of accidents, specifically that involve weapons of various sorts. There are handgun, or knives or things like that.

That data was available historically, but I believe in the late '80s and early '90s that essentially was not used anymore. So that the full description of a death and then comparability with NCHS data again is difficult when you don't have those pieces of information.

I would like to recognize the co-author on this report, Commander Richard Kennedy who is the public health service officer assigned to NIOSH in one of their Morgantown facilities.

I would also like to recognize Lynn Jenkins, senior scientist with NIOSH who is representing NIOSH Officially today.

And I might add, this is somewhat of a unique publication in that it was co-sponsored by CDC and the Department of Defense. And it was kind

of closure, if you will, to my work at -- on active duty and with NIOSH. But I think a co-publication supported by both Assistant Secretary Joseph and Linda Rosenstock, the head of NIOSH is commendable and I think it shows a collaborative working relationship that should be continued.

I will certainly address any questions or comments.

COL FOGELMAN: Questions?

PARTICIPANT: Does this include overseas, out of the country?

DR. HELMKAMP: Yes. Eventually a 1300 is filled out on everybody. It may take a little bit more time, but it's incumbent upon each service through their individual casualty offices to submit -- I believe it's on a monthly basis -- to centralized office in Washington. But it covers deaths worldwide.

Yes, sir.

LT COL ECKERT: Lieutenant Colonel Eckert for the Air Force. In strumming through some of these pie charts it's striking to me that in almost all the services the homicide rate of women exceeds the suicide rate. And there's certainly been a

number of efforts recently to prevent suicides, but I have not heard anything about preventing homicides in women.

DR. HELMKAMP: That's true. Also, I'm not -- I don't think I bring it out in this publication, but one that I've published on homicide in military medicine in '95 in fact the homicide rate among women where women are the victims is higher than among women in the civilian population. Not significantly so, but nonetheless higher. And it's also higher than among men on active duty.

I think a lot of these homicides are -- again, although there are not very many of them -- are an extension of domestic violence. And not many of them occur in the workplace, although some have. But I think that is an area that ought to be of concern as well as suicide.

DR. FLETCHER: That's the point I was going to make also.

Question, is fratricide included in here? I haven't read it. Friendly fire? Friendly fire, is this included?

DR. HELMKAMP: That would be an accidental category. As a matter of fact, one of the papers I

wrote on this on the Persian Gulf War published in JOM three years ago brought out a discussion on friendly fire.

COL FOGELMAN: Other questions?

(No response.)

COL FOGELMAN: Okay. Thank you very much.

(Applause.)

COL FOGELMAN: We'll have some copies in the office. If you need extra copies let us know and we can send them to you later.

We're going to take a break now until about 2:20.

(Whereupon, at 2:05 p.m., a brief recess was taken.)

COL FOGELMAN: Okay. If I could have your attention please. One administrative announcement, please. The court reporter says she's unable to pick up your names when you are speaking, so please, before you say anything tell them who you are in the microphone so she can pick that up.

It helps for our transcription and also when I'm trying to go back and read it later so I know who's talking.

Our next speaker is going to be Captain

Steve Cunnion who is an assistant professor at the Department of Preventive Medicine USUHS, the Uniformed Military Medical School. And he's going to talk to us about the USUHS data analysis center.

CAPT CUNNION: Good afternoon. My name is Steve Cunnion, C-u-n-n-i-o-n. Just to make sure that's recorded.

Thank you for being here today. I always appreciate talking in front of the EPI Board. Today Dr. John Gardner and myself would like to brief you on a proposed center that we're trying to start at ESUHS to try to solve some of the surveillance problems and database problems that exist in a tri-service environment.

We're trying to be sort of the EPPI center of epidemiology for the military. And if Pat Kelley doesn't get too offended, if he's Aunt SARA we'd like to be Uncle EPPI.

And this is what we're going to propose.

(Slide shown.)

CAPT CUNNION: First of all the present needs in tri-service environment are listed here or that we feel are some of the need are listed here.

One is a place where central analysis can be done on the different DOD databases, also a center that has some sort of epidemiological oversight on the various databases. A place where there's really a think tank devoted to military medical problems, a center for someplace where we can do projections and simulations on military medical scenarios and also a place where we can do some training modules for readiness in military medical problems that we get called on to do.

(Slide shown.)

CAPT CUNNION: So in the first one the biggest problem we've always had in military databases is trying to merge them together and we found that it's very time consuming and very costly and, of course, having a problem with turf and ownership and publication rights and everything like that.

There is some software now available that can be modified for servers on the Internet that we can actually do database mergers in a virtual reality setting. We can -- in prior set up with people make agreements what databases can be -- what fields and what databases can be extracted and if

they're on a mainframe computer with Internet access it's very easy. It's a relatively easy computer software problem to go in and extract those data in those fields that are capable of -- that have been agreed upon to be extracted and set up databases using five or six different databases at the same time.

So, what we'd like to do, we want to help the other centers out. I say we want to be the EPPI center. We want to -- the whole purpose of this center is to provide tools and a thinking tank for all of the centers to be working together.

The other problem we have with an oversight is someone -- we all know that there's problems with our databases and if you have -- if you want an outside opinion on your database and how it needs to be verified or the coherents of it, we are available to do things like that.

(Slide shown.)

CAPT CUNNION: So, on that basis we would -- USUHS would be a base for surveillance research and validation studies, also for special analysis on specific DOD requests and also the core faculty. We have essentially agreement with to be able to use

entire faculty at USUHS for all four services they're there through both the dean of the medical school and the president of the university.

(Slide shown.)

CAPT CUNNION: And the real purpose for the think tank is to become a seed to develop a military war college. All the other services that have war colleges do -- to act as think tanks and we have nothing really available in the military and we'd like to use this center as the seed to begin that process.

(Slide shown.)

CAPT CUNNION: When it comes to medical projections, simulations, and surveillance development we do have a faculty of military epidemiologists. We'd like to be involved in long-term analysis both strategic and tactical use. We are not interested in doing the, it's due tomorrow, or due yesterday type of scenario like occurs in many of the problems that we run in the military where somebody needs the data instantly. We're more interested in doing long-range analyses and projections.

But we're willing to train people to do

short-term analyses when necessary.

(Slide shown.)

CAPT CUNNION: So, in this case there is some software decisionmaking. There's some decisionmaking software out there that can address specific policy and medical or tactical issues utilizing the DOD databases and also there's an analysis program that allows for free thinking simulations and involving problems that you have no firm data on. You can still do decision-tree analysis figuring out -- estimating your own needs when the database isn't there and finding out what the outcome will be.

(Slide shown.)

CAPT CUNNION: Also with this computer concept we're much into helping out -- we're training because we are a university. We have a lot of teachers there and a lot of people who like to teach and to develop interactive CDs through the Internet, both combination CD and the Internet to provide Just-in-Time training.

(Slide shown.)

CAPT CUNNION: So all these principles are really based on just two different approaches using

software. One is the capability of an Internet server program to virtually merge DOD databases of any type. And a decision-analysis software that we can use for making planning tools, projection, simulation, training and also a management tools.

(Slide shown.)

CAPT CUNNION: So in that case we can provide a quad-service expertise in all areas of military medicine, have the capability of merging DOD databases, have professional consultants of DOD database of validity, be able to do health care data research in evidence-based medicine, and essentially provide those type of consultations that some people don't have time to do.

We want to also provide the think tank atmosphere, computer tools for decisionmakers, training tools, simulations for war games and other than war scenarios, and courseware in just-in-time training.

And I'm like 10 minutes.

COL FOGELMAN: Uh-huh. Could we have the lights, please?

CAPT CUNNION: That's all there is. We're just starting. We don't have any money yet. We're

looking for some creative financing. We're under the new military policy we're sort of a fee-for-service type center. And we're looking for plank owners. And that would be we're planning on five. If we can get five plank owners, five people who originally -- five organizations originally built to buy in on this at about 100K a piece a year, we'll guarantee them whatever services they need. And they will get priority over anyone who wants to come in later for our services.

Any questions?

DR. ANDERSON: Yeah, how -- how do you intend to handle confidentiality of medical records issues that you've got a think tank sitting around will they have access to personal identifiers or --

CAPT CUNNION: No, what -- as we borrow from databases we'll be setting up a field in those databases with the unique -- with the unique coding identifier. And so they'll be know -- the database will be known as a person, but we won't know their name or anything like that.

DR. ANDERSON: And the security on the Internet?

CAPT CUNNION: It's quite feasible now.

It's not a problem.

DR. STEVENS: I'm not sure how you -- I guess that anyone can use this whether they have any idea how to use data or not. It seems to me that there's the potential for people coming to very strange conclusions as they often do with N. Haines when they don't know how to use that database. There's no way that you can control what sorts of peculiar analyses people choose to do in public by this --

CAPT CUNNION: No, it's not going to be accessed by anybody but -- we have the capability of only accessing it. And we're doing it for someone else who is paying us to look at something.

DR. STEVENS: I see. So it won't be open to anybody who can get on the web?

CAPT CUNNION: No. No, no, no. No. No.

DR. FLETCHER: Please identify yourself as you speak.

DR. STEVENS: Cladd Stevens. It's not clear to me what data you're actually going to put into this system?

CAPT CUNNION: It can be any database from any dataset. Whether you're talking about health

promotion type stuff, whether you're talking about deaths, whether you're talking about accidents, whether you're talking about IC9 codes, anything that can be put in a database can be -- can be extracted through the Internet and looked at.

Now, we're not going to be doing this blindly. I mean, people will say, hey, the three of us have this data, we'd like to have some information of our three databases looked at, but we don't have the time or the money to merge these things and look at them, will you do that for us. And they will work with that. And we will show that -- we will set it up so these three databases can be merged and they can look and we will help them with the database.

DR. STEVENS: So you're not going to do this all up front, you're going to take specific questions and then go --

CAPT CUNNION: Yeah, this is fee for service. We -- we -- it's not an academic center. It is essentially a fee-for-service center. We're going to do jobs for anybody whether it's operational medicine or tactical or strategic needs.

DR. FLETCHER: Other questions? Dr. Broome?

DR. BROOME: Dr. Jones, it seems to me that the injury work group had a great deal of experience looking at the different types of at least the medical databases and could you comment on whether the biggest problems are with access, with incompatibility of coding, presumably they all at least do use social security numbers so you have an identifier you can use to link. But what -- in your experience how would this kind of facility help or not help your objective of having better injury surveillance data?

COL JONES: Well, let's see here -- can you hear me?

I think certainly what we're talking about here as a concept is doable. I think that they're talking more about -- I mean, the way that I would envision this is this would be a research resource that would capitalize on surveillance resources.

The biggest obstacle has just been simply the vision to take the existing databases which are largely administrative and start using them for surveillance purposes.

We have a large number of databases as you've pointed out, deaths, disabilities, even hospitalizations have not been routinely used for surveillance. And they have core elements. All of those -- the ones that I've just named all have standardized coding systems. And the disabilities uses a VA coding system for disabilities, rating disabilities. Hospitalizations, of course, use ICD9 and they all have social security numbers in. So theoretically you could link all of these. Plus you can link population data.

So what we're talking about here is doable.

DR. BROOME: But are the access issues and concerns of confidentiality who would have to give permission for this kind of merging?

COL JONES: Well, I think within the services certainly agreements could be worked out. I think the main thing would be protecting -- given that we're going to transmit these, you know, probably electronically eventually you'd have to work out the security issues. But I think, you know, that the services could work it out.

This, of course, involves more than just medical databases. We're talking about personnel

and other departments. But we've already worked our arrangements like that. For instance, the Army Medical Surveillance Activity gets DMDC personnel data and hospitalization data as it is right now and some other data. So I don't see those issues as being a constraint once we figure out how we're going to do it and develop a plan.

But that's anticipating something I thought I was --

CAPT CUNNION: Remember, we'll be working with the people who own the databases. We're not going to be doing this, you know, without working with the people that own the databases. It's not that we're -- you know, we're doing this blindly on the outside. We are providing a service to people who want to look at different databases in a joint environment.

COL GARDNER: I'm Colonel Gardner. I think that's the point here is that through the injury work group we've looked at, at least a dozen different databases and found incompatibilities between them all and found them all difficult to assess and there's been a lot of talk about consolidating everything in a uniform coding system.

And that's such an overwhelming task that nobody will attempt it.

And what we're trying to do is say, hey, look, you don't really have to pull all the data together in one place in one big huge computer system. Instead you can extract what you need from the various places, pull that together and then work out the coding problems and deal with the issues on a smaller scale. And that's the type of thing that we're trying to propose.

DR. FLETCHER: Other questions? Comments?

(No response.)

COL FOGELMAN: Thank you very much.

Okay. Our next speaker is Bob DeFraites. Lieutenant Colonel Bob DeFraites is staff preventive medicine officer at the Office of The Army Surgeon General. And he's going to bring up a question for the Board on whether or not HAVRIX and VAQTA hepatitis A vaccines can be used interchangeably.

DR. DeFRAITES: Thank you, Colonel Fogelman. Thanks. Let's see, is there a pointer up here?

COL FOGELMAN: There should be a laser

pointer up there on the -- there was a laser pointer. If somebody took the laser pointer please return it.

DR. DeFRAITES: Oh, here it is, here it is, here it is.

Could I have the first slide please?

COL FOGELMAN: Bob, I think the overhead is on.

DR. DeFRAITES: Oh.

(Slide shown.)

DR. DeFRAITES: Yeah, it's my pleasure to -- to help guide the discussion and the deliberations of the Board on this issue of the hepatitis A vaccines are they interchangeable. And before I go any further, I want to say first of all as a disclaimer that these opinions and discussions that I'm going to lead represent my own opinions and don't -- shouldn't be construed to represent those of the Department of Army or Department of Defense.

(Laughter.)

DR. DeFRAITES: And secondly, I'd like to thank the efforts of Merck -- representatives of Merck and Company and Smith-Kline Beecham. I appreciated the attention that I received from both

of those companies with the knowledge that I was giving this presentation and hopefully if there is a life after the military maybe with one or both of those organizations --

(Laughter.)

DR. DeFRAITES: I think -- I think it may go one way or the other and I might seal my fate today.

Let's go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: Well, certainly hepatitis A has long since been recognized to be a threat to the U.S. military since -- especially since the outbreaks of camp jaundice were recognized as far back as the Civil War.

In general we recognize hepatitis A as a threat to our forces wherever they deploy and where the food and water hygiene might be compromised.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: This map shows those areas of the world that are generally thought to be at higher risk and were constrained by sort of the political boundaries here, but in general Central

and South America, other developing countries in Asia and Africa are considered to be at higher risk with those areas at lower risk in Australia, Japan, Western Europe and the U.S.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: Historically immune globulin has been the prophylaxis of choice for troops during deployment. This has been, you know, an extensive practice throughout the DOD and in general our rates of hepatitis A during deployments have been historically very low.

We know of no cases of hepatitis A for example during DESERT SHIELD and DESERT STORM. Mainly probably through the use of immune globulin. I think some of the other coalition forces had some case of hepatitis A during that conflict.

Now, in the last several years the situation has changed dramatically with the licensure of the first hepatitis A active vaccine which was Havrix. That's a Smith-Kline Beecham product which was licensed in 1995. And now this year as if we couldn't get too much of a good thing Vaqta which is the Merck product was licensed

earlier this year.

Let's go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: The issues surrounding interchangeability are those as follows -- especially for the military, but I think all travelers are going to be faced with these same type of difficulties. For both vaccines that are licensed now there is an interval between the primary and the booster dose of six to 12 months.

Military personnel certainly may receive the doses at different locations. In other words you could receive your first dose at one place and then go to another location for the second dose. Both vaccines are available at very similar prices. And the question for us is can vaccine B be used to complete the immunization series started with vaccine A?

Many times in our immunization records we don't record the manufacturer of the vaccine. It will just be recorded, as one can imagine, as hepatitis A vaccine.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: What I'm going to discuss are some of the general characteristics of these vaccines and both of them are formal and inactivated vaccines that require -- because they're inactivated usually that implies that they require more than one dose as I've already mentioned.

I'm going to show you some of the immunogenisity safety and efficacy data for both of the vaccines. Talk a little bit about some limitations of these vaccines. And then we have -- I have a little bit of data on comparison of immunogenisity between the two and then address such as the data errors are available today on the issue directly on interchangeability.

Let's go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: Now, the following few slides were provided by Smith-Kline Beecham and I decided to go with Havrix first since it came first in the alphabet. And I don't know where the name Vaqta came from. If somebody can tell me, I'd -- you know, if they -- if they invent another vaccine they should pick the letter that comes in the alphabet before the other one so that they'll get

talked about first. Though it may be that being discussed last is an advantage.

Anyway, Havrix is produced the -- it's derived from an HM175 strain. This hepatitis A virus is -- was isolated from a human case in Australia in 1976. And it's raised an MRC-5 human diploid cells as a -- the production process includes freeze/thaw, some purifications steps and then formal and inactivation, adding of alum adjuvant and two phenoxym ethanol as a preservative.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: The dosing regimen is different for adults than it is for children. The vaccine that's licensed in the United States is a 1440 elisa unit vaccine. This elisa unit is a measure of potency of the Smith-Kline vaccine.

The primary course is called -- well, it's one dose at month zero and then a second -- the booster dose for adults is given at months six to 12. There's a lot of variability. It can be given as early as month six and as late as month 12. It comes as prefilled syringes or one-dose vials. And

it's an IM injectable vaccine.

Now, this pediatric dose, actually there's another formulation -- a newer formulation available. This chart shows the formulation as a 360 elisa unit for children and there's a -- whoops -- there's a three-dose series, zero, one, and six to 12 to months for the booster dose.

There's a new formulation, a two-dose -- with a two-dose series for children at months 0 and six to 12 with a 720 elisa unit. So this chart actually doesn't show the other newer formulation.

I'm going to focus, for the most part, on the adult regimen since that's what's of significance to us for military purposes.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: As far as the adverse reactions recorded with Havrix, soreness at the injection site is recorded in up to 56 percent of adults, 15 percent of children. The -- the more systemic symptoms like headaches about 14 percent, and then there's a variety of other -- other minor side effects with an instance of 1 to 10 percent.

Let's go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: In general the typical profile you expect with formal and inactivated vaccines in general.

Now, this slide shows some immunogenisity data. There are two charts here. The one on the left is a chart showing the immunogenisity of immune globulin and the other one on the right is Havrix.

The green bars -- both of these charts have similar scales. So they're directly comparable. The green bars are meant to represent the percent of immunized persons with detectable antibody. And so for immune globulin at day five after the injection over 90 percent have detectable antibody at least with a modification of the standard HAV/AB test a much more sensitive antibody test 90 percent of persons have detectable antibody. That number decreases to 42 percent by just two months after immune globulin. No surprises there.

And you can see that the geometric mean titer which is shown in the orange bars never goes above 100 mili-international units per milliliter. On the other hand, the active immunization with a

primary dose at day zero, by day 15 GMTs are in a range of two to 300 with 88 percent of recipients showing detectable antibody. That percentage rises to virtually 100 percent by the end of the first month after the first dose and then there's a second dose given at month six.

Could we try to focus that a little bit better?

Second dose at month six. What this second dose essentially does, it doesn't really increase the number of -- the proportion of recipients developing any antibody, but it does give a tremendous boost. This is a broken line, the GMT here is in the 4,000 range.

And that's the function of this second dose at six months is to really give a solid boost to the geometric mean titer. So the differences between the two, as you can see, immune globulin even though it gives an early, almost immediate effect, gets an immediate detectable antibody that wanes quickly. On the other hand active immunization especially with a six-month booster rises titers to the 4,000 range which are considered to be extrapolated out to give protective antibody for a dozen years or so.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: Though we don't know exactly how long it will protect.

This vaccine was subjected to an extensive efficacy trial in Kompon Pet Province [phonetic] in Thailand. It was led by Colonel Bruce McInnis who is here at WRAIR. There were 40,000 children enrolled, ages 1 to 16 years. It was a randomized double blind study. Half the -- half the children received the Havrix. Actually this was the 350 elisa unit vaccine. The other half, the control units, received Engerix hepatitis B vaccine.

The vaccine schedule was at zero, one and 12 months. Surveillance for cases of hepatitis A began four months after the first dose. So there's no data on early efficacy, but on efficacy from four to 12 months.

Go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: For symptomatic cases there were 32 symptomatic cases of hepatitis A among the 18,000 recipients of the hep B vaccine the control arm there were two symptomatic cases of hepatitis A

in the vaccine -- in the group that received hepatitis A vaccine. The protective efficacy was calculated at 94 percent with confidence intervals of 82 to 98 percent.

When subclinical cases were added, there were two additional cases that had some evidence perhaps suggestive of subclinical hepatitis A were added to the group that had occurred in the vaccine group. That lowered the efficacy to about 84 percent. The confidence intervals around that were, I think, 60 to 90 percent. If you include the subclinical cases.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: This slides shows the effect of simultaneously administering immune globulin with Havrix. And what you -- and this slide shows in the first row the effect of giving immune globulin alone and then giving the second row is the Havrix alone and here's the combination.

These first two rows essentially reflect what I showed in that bar slide from a few slides ago. Early on you get 100 percent of recipients of immune globulin have detectable antibody whereas by

day five nobody who receives Havrix alone has detectable antibody. Well, that's remedied by giving both together. You get the early immune response, the early immune protection with the immune globulin. What that does, the net effect, though is blunting somewhat the GMTs. You get nice sero conversion rates, but it does seem the history has been that giving immune globulin concomitantly with active immunization seems to blunt the geometric mean titers.

This group got a second dose at month six and their GMTs were 2,211 versus 3,967. So it did blunt the immune response to the active immunization. That's a little bit of a disadvantage of giving immune globulin concurrently.

The package -- I'll address this later on, but right now the package insert indicates that if travelers expect to be exposed to hepatitis A in two weeks or less that immune globulin should be given along with their first dose of vaccine.

Let's go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: These slides -- these next few slides I'm going to be discussing Vaqta which is

the Merck vaccine. And these slides were provided by Merck.

Vaqta is also an inactivated whole virus vaccine. It also uses MRC-5 diploid fiber blast.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: The seed virus is a Costa Rican strain isolated in, I think, 1966 in Costa Rica 326-F and it undergoes purification, formal and activated and activation alum as an agivent and final bulk product.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: The dosing schedule for Vaqta for adults is one dose at day zero and the second dose given six months after the first dose. This dose can be given as early as five months and as late as seven months.

For children it's a two-dose series. The first dose can be given at -- is given at day zero and the second dose can be given between six and 18 months after the first dose.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: The safety of Vaqta is similar to the Havrix vaccine. In general there's been no serious vaccine adverse effects during the clinical trials. In 2,600 healthy children serious -- I guess, not serious, systemic complaints of fever, headache, abdominal pain and pharyngitis have been relatively -- relatively rare. In 1500 adults, again, headaches, about 16 percent. That's very similar to the data for Havrix. Fatigue 4 percent, et cetera.

So it's a similar safety profile, at least from these data as Havrix.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: I know I'm going to hear some discussion about that, but we'll wait for that to come.

The immunogenisity of Vaqta, again, based on -- this is a single dose of Vaqta four weeks post-injection, 97 percent of children have detectable antibody, and 95 percent of adults.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: This was -- this vaccine

actually was the first to have -- to be shown to efficacious. There was an efficacy trial performed in Monroe, New York in Curious Joel which is a Hasidic Jewish community which had experienced frequent and recurrent outbreaks of hepatitis A on a seasonal basis relatively predictably over several years. Children were enrolled in the study. They were either given -- randomized to receive the Vaqta, 25 units which is one half the potency of the adult formulation or to receive an alum with -- alum with diluent [phonetic] as a placebo.

The composition of the study groups was very similar. And they were followed up for slightly over 100 days after the first dose.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: So whereas the Havrix efficacy trial started follow up at four months, the Monroe trial ended almost at four months.

This shows you the cases that occurred in the vaccine and the placebo groups. On the left-hand -- the Y axis is the number of cases of hepatitis A and on the Y -- on the X axis is days out through day 140.

This shadowbox here ending at day 50 represents the incubation period for hepatitis A. Day zero is the day that vaccine recipients and placebo recipients received their first dose.

The gray bars show active cases that occurred in the placebo group and the black bars show the cases that occurred in the vaccine group. Note that no cases occurred in the vaccine group after day 16 following their first dose. So there was active, you know, hepatitis A in this community throughout this study.

And, again, the study was ended at day -- at day 105, the code was broken.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: Oh, go back. I'm sorry.

Of course, the efficacy -- the main endpoint of the trial was the efficacy from day 50 on out and of course that efficacy was 100 percent.

And you can see that there were no cases -- as I mentioned cases beyond day 16. So highly efficacious vaccine.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: This shows you the impact of this immunization program on the Curious -- on transmission of hepatitis A in the Curious Joel community.

Now, what happened during the study is that the phase one of the study -- the study was unblinded at, you know, four months after it began to allow other placebo recipients to receive active vaccine. And you can see that just introducing this vaccine in the community essentially extinguished the transmission of hepatitis A. There were new cases introduced but none of these cases that occurred in the years following the study were in the community at the time of the vaccine trial. These were all introduced cases.

And you can that never again did hepatitis A take hold in this community.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: The other question relative to the protection of these two types of vaccines to worldwide -- to hepatitis A that occurs worldwide is the idea that there's a tremendous amount of -- a

considerable amount of genetic diversity in hepatitis A strains. There are at least four different genotypes that have been described for human hepatitis A. Both of the strains, the HM-175 and the CR-326 are members or are in the genotype one. And there are different sub-genotypes but they're both genotype one.

However, the clinical significance of this is very limited in a sense that antibody from immune globulin has been shown to protect against hepatitis A worldwide. There does not seem to be any difference in agnogenic characteristics between these genotypes, at least not of any clinical significance yet. And certainly antibody from these vaccines appears to be protective against all strains of hepatitis -- human hepatitis A that have been tested.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: Some of the limitations that I wanted to mention. First of all is this for military purposes especially, but I think for all travels is this delay and onset of protection. And the idea that there is -- does seem to be some delay

in developing antibody too and active immunization.

However, the use of ISG now especially is curtailed because of the limited market for ISG and some of the difficulties we've had in procuring it. If at all possible it would be -- it would be a wonderful step forward if we could do away with the need for controlled administration of ISG. If for no other reason then to -- the effect it might have on long-term protection if it blunts the geometric mean titers to the active immunization perhaps the duration of protection may not be as long in people who received the original dose with ISG.

And the second question is the duration of protection after the first dose. It's very significant for military purposes in situations where we may have troops deploying on a deployment that may go beyond six to eight months for a year or more, and only able to get one dose before they depart. And the question is, how protective is that single dose? And these are questions that I don't have answers for today.

Let's go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: Now, there have been no

head-to-head studies of the two vaccines comparing immunogenisity. However, there are data from two studies with a very similar design that were performed at WRAIR between 1991 and '92 among about 150 seronegative U.S. soldiers. One study was done using an earlier version of Havrix, the 720 elisa unit dose at Fort Lewis Washington and the other one was a study using Vaqta at Scofield Barracks, Hawaii.

Both groups that I'm going to show you data from received two doses of the vaccine -- of whatever vaccine they had -- they received two doses, one in each arm. So, essentially the adult -- modern-day adult equivalent -- roughly equivalent of what you would receive with Havrix today. Two doses on day zero and then we got blood -- serum was drawn on day 14 and then months one, two, six, eight and 12. And then both of these sera were run using an IMX assay here at WRAIR just to show that -- just to have them comparable. So they're run in the same lab at the same time.

Go to the next slide, please?

(Slide shown.)

DR. DeFRAITES: This first slide shows you

the percent of vaccine recipients that had detectable antibody at a half a month, one month, et cetera. And as I mentioned the first blood draw was at day 14 which is this half-month level. And then they got blood drawn at month, one, two, six, eight, and 12.

And you can see here, it shows you -- and the white, solid line is a Smith-Kline Beecham product and then Merck vaccine is shown in this broken, dotted line. So in general anywhere between 40 to 80 percent by day 15 received -- had detectable antibody by this assay. And we used a cut off at least 20 mili-international units per ML of antibody to be considered to be sero positive.

You can see after this single dose that antibody titers -- one they -- I mean sero conversion once it occurred remained fairly constant. You lost a couple of your sero conversions reconverted back to the sero negative, but not very many. By the end of the 12-month follow up over 60 percent still had detectable antibody by this assay after the first dose.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: This shows you, it's not geometric mean antibody titer, but it's a median antibody level. Again with the dose on day zero the Merck product is shown in the dotted line and the solid line is the Smith-Kline Beecham. And this just shows you that by day 14 anywhere between the median antibody level was a little less than 20 for the Smith-Kline Beecham product and a little over 40 for the Merck. And, again, the GMT, after it stabilized at about one month pretty much stayed constant for the rest of the duration studies.

So this is really the only data that I know of where both of these vaccines are being looked at, at the same time in similar populations with the same assay.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: The trouble is they're not -- next slide, please?

(Slide shown.)

DR. DeFRAITES: The trouble is, these vaccines are not the presently-available licensed vaccines necessarily.

Now, there have been some data directly on

this -- addressing at least one half of the equation on giving a booster of one vaccine -- of a second vaccine after starting the immunization with vaccine A. So Vaqta -- this data was provided by Merck. And as shown a group of personnel that -- I'm sorry, they were given Havrix first and then boosted with Vaqta.

There were 43 participants that received a single dose of Havrix on day zero and then they got a second dose of vaccine. The Vaqta was given anywhere between five and 19 months later.

They had antibody drawn after they received their second dose. Presumably they were sero negative before they received their first dose. But they had serum obtained anywhere between seven and 21 months after the first dose. This -- this line -- this phrase is a little misleading. They only had blood drawn once and that was soon after they received their booster. So what you are seeing on the next slide is going to be antibody levels done after boosting. And this was the antibody is expressed as a modified HAVAB. The HAVAB is a standard assay to show immunity to hepatitis A after natural infection. A modification of this assay

allows it to be much more sensitive.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: Those antibodies levels again after immunization are usually much lower than those found after natural infection with hepatitis A.

Here you see the group up at top. These are the 43 individuals here that received Havrix followed by Vaqta. After -- after receiving their booster dose all 43 individuals had antibody. The GMT was in the range of 2500 mili-international units per ML.

There's a historical comparison group here. These are Vaqta recipients that received the usual dose of Vaqta at zero and six months. At seven months after the first dose, or again shortly after the sixth month dose 100 percent of them had antibody. This is what the GMT in this group was, 5,880. Five months later they didn't receive another dose, but five months later 96 percent still had detectable antibody. The GMT had dropped down to 16- 1700. So you can see that after this not really direct comparison, but the GMT is comparable

when you receive Vaqta as a second dose as when you receive Vaqta as the full series.

So it does look like, at least that Havrix does prime you for the second dose of Vaqta. Whether it works the other way around is a matter of speculation right now.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: In conclusion I think we can judge that both vaccines are safe, immunogenic and quite efficacious.

The limited data that we have do support the concept of cross-protection and interchangeability.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: The recommendation is -- for the AFEB is to allow vaccines to be interchangeable and perhaps to recommend a study where the recipients would be randomized to receive in a direct head-to-head comparison either Vaqta alone and Havrix or Vaqta first followed by Havrix, and Havrix first followed by Vaqta.

Next slide, please?

(Slide shown.)

DR. DeFRAITES: And my final unofficial recommendation because I don't think it works this way is for the DOD to purchase one vaccine brand, have sealed bids, the winner of the low prices takes all for five years and we wouldn't have to worry about interchangeability.

Pending your questions that concludes my --

COL FOGELMAN: Can we have the lights please?

DR. FLETCHER: Thank you. Very good.

COL FOGELMAN: Questions?

DR. FLETCHER: Dr. Stevens?

DR. STEVENS: I'm assuming -- I'm assuming that your interchangeability question is limited to the issue of whether you could give a different vaccine for the booster dose. You're not talking about an issue of whether they're comparable in that early immunization period?

DR. DeFRAITES: Both.

DR. STEVENS: Both.

DR. DeFRAITES: The question -- the real question of interest to the field is are these products like hepatitis B vaccines in a sense it

doesn't matter which one you -- you start with one and you mix and match, at least for adults. That's the question.

DR. STEVENS: You mentioned that the Havrix vaccine -- the company, Smith-Kline recommends that if you're going -- if you're not immunized but you're going right away to a high-risk setting that you will also be given immune globulin?

DR. DeFRAITES: That's true for both vaccines. Both vaccines say the same thing in the package insert. I don't know -- someone from Merck can correct me on this, but I believe both say two weeks.

DR. STEVENS: The one thing that I think is really apparent -- at least to me, is that that's probably being overly cautious and I would -- I bet it's not necessary. And the reason I say that is based on the data from the Monroe trial where there were cases in the vaccine group in the first 16 days. But the incubation period for Hepatitis A traditionally is 20 to 50 days. And so more than likely those were people who were exposed to the virus before they even got the vaccine. I would bet this is perfectly fine by itself.

DR. DeFRAITES: That's with the assumption that in the trial that these were --

DR. STEVENS: I'm not saying that you can go against the insert -- package inserts, but I would -- obviously you have a disadvantage in a sense with the Smith-Kline vaccine because you don't have that data on early immunization. But it's clear that these are two highly effective vaccines even with a single dose. And my answer would be I agree with your recommendation.

COL FOGELMAN: That was Dr. Stevens for the record.

DR. FLETCHER: Dr. Clements?

DR. CLEMENTS: This is Dr. Clements. I totally agree. I think with that long incubation period that -- you know, that in the meantime even after exposure that you're going to already be primed with the immunizations. I know that they're not confident enough to make that recommendation, but it seems to me that -- that that two-week window is going to be okay.

DR. DeFRAITES: The other thing that seems to be true is that it appears that persons after they are shown to sero convert to the vaccine and

later lose antibody upon a booster dose, even if they don't have detectable antibody at the time, they develop a very nice anamnestic response. The question would be how lucky do you feel? You know, if you're exposed to hepatitis A and you don't have detectable antibody would the -- the anemenestic response protect you in cases where you'd be exposed to a wild type virus. I think probably yes, based on the incubation period of hepatitis A.

But it's a real question for us for the military because getting people -- getting ISG and hepatitis A vaccine at the same place at the same time for what might not be indicated is a real problem.

DR. FLETCHER: Dr. Clements again.

DR. CLEMENTS: Yes. I'm curious as to how often you would be reimmunizing with the passive immuno globulin because if 42 percent have already lost a protective level of antibody by two months, you know, maybe -- maybe --

DR. DeFRAITES: What do you mean? I mean, --

DR. CLEMENTS: Because you do have -- because in the same case with the vaccine, if you

have immunologic memory and you can mount an amnestic response, then you might well be protected -- still protected.

DR. DeFRAITES: I don't know if I understand the question.

DR. CLEMENTS: How long -- how often do you re-immunize with the immuno globulin?

DR. DeFRAITES: ISG?

DR. CLEMENTS: Yes.

DR. DeFRAITES: Immune globulin?

DR. CLEMENTS: Yes.

DR. DeFRAITES: If you give two MLs we -- our recommendation is that two MLs of IG for an average adult recommend reimmunizing at three months.

If you give 5 MLs, then four months -- four to five months. That's the standard recommendation.

I did want to mention part of your hand -- one of the handouts that arrived probably at lunch time is the DOD's policy as expressed by Dr. Joseph and that is by December 31st, 1998 to immunize the entire active and selective reserve force with hepatitis A vaccine.

And so this question is going to be very

much a bigger issue of us in the future as we go to mobilized to full immunization.

DR. FLETCHER: Dr. Polland?

DR. POLLAND: I agree with your conclusions. However, there is no data to suggest that there isn't a reason that they aren't interchangeable not even any anecdotal data of vaccine failure when that has happened.

The other thing is, I'm not aware of any vaccine model, you know, same vaccine but different manufacturers or brands that aren't interchangeable.

And lastly, there's just one thing I wanted to check on, you made the statement that manufacturers now record it. My understanding is that federal law requires that you record manufacturer, lot number, a host of other things too.

DR. DeFRAITES: We would like to say that that's true. I mean, we try to encourage people to do that. I can tell you that it doesn't always happen.

DR. FLETCHER: Dr. Waldman, I believe was next.

DR. WALDMAN: Yes. I just had one quick --

in the memo that you cited, the 12 August memo, there's a priority list of different categories of personnel and then the policy would be implemented. I just wanted to be clear, are your recommendations that you are making, are those for adults only or do those apply to children as well?

DR. DeFRAITES: Right now for adults only.

DR. WALDMAN: For adults only. So only a few of these categories would be -- your recommendations would apply to only -- it wouldn't apply to family members, for example?

DR. DeFRAITES: In terms of interchangeability?

DR. WALDMAN: I'm asking you the question because you --

DR. DeFRAITES: I would say, yes. I would --

DR. WALDMAN: -- gave the presentation.

DR. DeFRAITES: Right. I focused it mainly on the active -- on the adult population, but I think it could apply to children, too. I don't see why not. So I'd say yes.

DR. FLETCHER: Dr. Schaffner, do you have --

DR. SCHAFFNER: Well, I was just going to observe that large institutions such as mine are soon going to be in the same position that you are because vaccine is purchased by some remote consortium -- purchasing consortium. We don't know what brand of hepatitis B is in the pharmacy this year. I'm sure next year we won't be sure which brand of hepatitis A is in the pharmacy and I think we're going to be operating under the assumption that they're interchangeable.

DR. FLETCHER: Dr. Sokas?

DR. SOKAS: Yeah, I agree with that, but I wanted to get back to Dr. Polland's point which is that when we do it in civilian life you have a piece of paper that you have from the vial written on the lot number and the vial number and the person signs an informed consent there that stays in the chart. Partly, I guess, as a CYA thing that we always do, but also in case there is a problem with a lot of vaccine and somebody has to trace it down it's in the person's record.

DR. DeFRAITES: Well, what we're seeing -- what we're foreseeing is the likelihood that a military person will go from -- from Europe -- from

launch in Europe and then be transferred to Fort Bragg and whoever purchases vaccine at Fort Bragg will buy Merck product. And even though their chart says they received Havrix as the fist dose --

DR. SOKAS: Right.

DR. DeFRAITES: -- all we have is Vaqta. So do you get it or do you have to start all over again?

DR. SOKAS: No, no, no, no, we're not arguing that. We're saying it seems to everybody here that's interchangeable. That's not the problem. It's just that somewhere in the patient's record should be written that lot number for other purposes.

DR. DeFRAITES: Yes, that's true.

DR. FLETCHER: Dr. Clements?

DR. CLEMENTS: Yes, I just wonder if the companies have any data on a shorter interval? It seems like for military and even for travelers a shorter interval would be desirable. But I don't know if they have any data to look at a closer interval between the first and second immunization?

DR. DeFRAITES: It appears that the timing of the second dose is the important one. For both

of these vaccines one dose is sufficient to get a primary response in almost 100 percent of recipients. It's the timing of the second one to take advantage of the secondary immune response that's the important part and that's why you can't -- it seems like giving that second dose, for example, at one month you get -- you don't get the secondary response. You get more of a recruitment of the final few percent that didn't respond to the first dose. Actually it doesn't seem to make any difference because by one month practically 100 percent of people respond to that primary immunization.

The purpose of the second dose is for the booster effect and that's why the timing -- it seems like we're not sure how soon you can give it, but it seems to be somewhere around six months. Now, it doesn't seem to matter that much if you delay longer. It doesn't seem to affect that if you get an nice anamnestic response anyway the longer you wait. It's not -- but we would like to have -- be able to do this in one dose. Actually that would be great.

Second to that would be shortening that

interval in which you could be sure that you're getting the secondary immune response, getting that anamnestic booster response with the high GMTs assures you that you've got antibody for a long period of time afterwards. If you give that second dose too soon, you don't get that nice boost.

And that time -- I know Merck has data for month two at two months after -- that seems to be too soon, and five months seems to be enough time. And I don't know if you can bracket it anymore. I asked if they have data at four months or 3.5 or there doesn't seem to be any data in that window.

I think in general these vaccines were pursued with the model of the hepatitis B immunization series in mind with a zero-, one- and six-month dose. And what's turned out is that booster dose is important for long-term protection.

DR. CLEMENTS: But I think now they find they can actually convince the schedule for hepatitis B so it's something just to keep in mind that it might be optimized for deployment purposes in the future or for military purposes.

DR. STEVENS: In that respect --

DR. FLETCHER: Dr. Stevens.

DR. STEVENS: Yeah, sorry. Cladd Stevens. In that respect in terms of your thinking about doing a study I would think a more interesting study might be to look at that particular issue of shortening the time for the boost from a practical point of view rather than the issue of whether there vaccines are really interchangeable.

DR. DeFRAITES: That would be nice to do.

DR. STEVENS: I really don't think that's much of an issue frankly.

COL FOGELMAN: Okay.

DR. FLETCHER: Other questions? Yes, please identify --

COL FOGELMAN: Would you come to the microphone.

DR. FLETCHER: Identify and microphone.

MS. TABBS: Thank you. My name is Janet Tabbs I'm with the vaccine division of Merck and I just wanted to make a comment as a consideration under your recommendation for procurement.

(Laughter.)

MS. TABBS: I think that --

DR. DeFRAITES: As I said, I was speaking

for myself. I don't represent --

MS. TABBS: Right.

DR. DeFRAITES: -- anybody in the procurement.

MS. TABBS: Absolutely.

DR. DeFRAITES: Nor do I influence them in any way.

(Laughter.)

MS. TABBS: Absolutely.

DR. DeFRAITES: I wish I could, but I can't.

MS. TABBS: But under the circumstances with their only being uniquely four manufacturers of vaccines and the issue that came up with adenovirus. I think that strong consideration should be given to some type of an appropriate dual award. The military is certainly going to be one of the primary sources for hepatitis A with this initiative and it's just something that I think should be considered.

DR. FLETCHER: Thank you. Other comments?

DR. GWALTNEY: Are we being asked --

DR. FLETCHER: Dr. Gwaltney.

DR. GWALTNEY: Excuse me. Gwaltney. Are we being asked to decide also whether one dose versus two doses?

COL FOGELMAN: No.

DR. DeFRAITES: No. you can comment if you like, sir.

DR. GWALTNEY: In relation to that question, I understood that there were 40 percent of people that had antibodies after the interval before the booster. I mean, 60 percent, excuse me, that 40 percent had lost antibody; is that correct?

DR. DeFRAITES: After what?

DR. GWALTNEY: After one dose and after six months or whatever?

DR. DeFRAITES: It varies with the studies.

DR. GWALTNEY: Well, roughly.

DR. DeFRAITES: This is Havrix or -- in general after you receive a first dose and you don't get a second dose, it varies with the different studies of when you start seeing people reconverting to sero negative after converting. It varies and a lot of it is determined by when you draw the blood and a lot of times we design these things and you can't tell when they --

DR. GWALTNEY: What figure at six months? How can people still have antibody six months after one injection?

DR. DeFRAITES: I thin the figure it varied with the different vaccines. I think 60 to 70 percent is probably --

DR. GWALTNEY: Sixty to 70?

DR. DeFRAITES: That's just that one study, though, that we did. I don't know if I could generalize to all the others.

DR. GWALTNEY: Well, my question is not what the GMT is, but how many of those 60 percent have a level that you consider protective?

DR. DeFRAITES: Well, that's just it, it's what exactly is protective? I'm not exactly clear.

DR. GWALTNEY: -- immunologic studies, you know, on terms of exposure and what antibody tends to protect you. I realize there's a range, there's a biologic range, but there must be some -- you know, with flu we say 1 to 40 as an average.

DR. DeFRAITES: Yes, sir. Obviously you don't need much because immune globulin gives you very lower titers of detectable antibody and yet it seemed it's certainly efficacious in the post-

exposure setting and also as prophylaxis. So you don't need to much. How much you need to protect you is unknown, but these figures of 10 to 20 mili-international units per ML of antibody or roughly the thresholds that people have used, I guess, for protection.

DR. GWALTNEY: So most of them that have antibody would be above the titers you get with immune globulin?

DR. DeFRAITES: That's right. When I talked about percent sero positive I was talking about those kind of thresholds.

DR. FLETCHER: Yes, please identify yourself. MR. SABAR: I am Jerry Sabar from Merck, I used to be from WRAIR. Jack, I think that everything is a little bit dependent on how you measure -- what assay you use, but if you use that modified Havab test which is a pretty sensitive test and the limit of detection on that is about 10 mili-international units per mil, below that the test is too variable to really say anything. I think most people in the field consider that a protective level. It's probably even there you could probably go down lower than that and it would be protective.

And at about six months before you are getting your boost, about 90 percent of the people will still have over 10 mili-international units.

So, I don't know the data for Smith-Kline, but it may be roughly the same.

DR. FLETCHER: Comments? Questions? Dr. Stevens?

DR. STEVENS: Just one question. In Steve Joseph's memo he mentions that the priority list here with a plan to have all of these individuals immunized by the end of '98, so two years from now. Is there a reason for that -- taking that long or what's the --

DR. DeFRAITES: Yeah. I think that December 31st, '98 refers to all active duty and selected reserve, not those priority groups.

DR. STEVENS: I read it as -- oh.

DR. DeFRAITES: Because that priority list, I think includes family members, too, doesn't it?

DR. STEVENS: Ah-hah.

DR. ALLEN: Yeah, but it's confusing because they're in the middle of it and then there's other --

DR. DeFRAITES: Well, that shows good

policy is just confusing. That's the way I --

(Laughter.)

DR. DeFRAITES: -- the rule of thumb I always use is you can interpret it how you wish. But the way I think the services have interpreted it a meaning all active duty and selected reserve will be immunized by the end of 1998.

Now, why did it take that long? I don't know where that -- the figure -- the date came from. I don't know, I can't answer that anyway.

DR. FLETCHER: Dr. Waldman?

DR. WALDMAN: Yeah, I just wanted to clarify exactly what the question is that's being -- does it have to do with only the first question, the interchangeability?

COL FOGELMAN: Yes.

DR. WALDMAN: Not with the recommendations for the proposed studies or for the procurement?

COL FOGELMAN: The question is, can the two vaccines be used interchangeably?

DR. DeFRAITES: That's the question. The rest is gravy. If you want to recommend other things, that's nice too.

DR. FLETCHER: Dr. Broome?

DR. BROOME: I think it's extremely likely they're interchangeable. I guess I'm wondering how difficult it is to just do a study and not have there be any residual haggling -- it seems to be an extremely easy study to do. So I would put that on the table as to whether it's worth documenting.

And then one other comment related to procurement. CDC has certainly been concerned about having reasonable competition in the vaccine field and we do have multiple contracts with different manufacturers presenting the same vaccines. It's kind of -- it has merit to --

DR. FLETCHER: Other comments? Questions?

(No response.)

DR. FLETCHER: Thank you very much.

COL FOGELMAN: Okay.

DR. DeFRAITES: Wait, I think we have one more -- one more question.

MR. ARCHER: Can you hear me?

DR. DeFRAITES: Yes.

MR. ARCHER: My name is Vint Archer and I'm with Smith-Kline Beecham pharmaceuticals and I'd like to address two points. One is to follow up on what my colleague from Merck said and that is due to

the limited manufacturing capabilities for a vaccine of this nature that I would suggest that DOD seriously look at the CDC model of the VSC program for a shared award procurement type of program. That seems to work quite well and I think that they feel it has been very successful.

The other thing was discussing the time interval between the initial shot and then the booster in terms of the compression of that and specifically with Havrix the booster dose is recommended from the six- to 12-month period. So really with the way the approved labeling is for the product, you can take it all the way out to 12 months before you have to give the booster dose. So the data supports that and I just don't -- I don't have the information about the compression. Thank you.

DR. FLETCHER: Other comments?

COL FOGELMAN: Okay. Thank you very much.

DR. FLETCHER: Thank you.

(Applause.)

COL FOGELMAN: Okay. The board will now move into executive session. I'd like the

preventive medicine officers to stay and anyone else that I talked to about staying earlier, please?

So we'll take a few minutes and -- take about three or four minutes here and we'll be ready to start again.

(Whereupon, at 3:28 p.m., a brief recess was taken.)

COL FOGELMAN: Okay. Everyone back, please.

Okay. Can we have everybody take their seats, please?

There are two -- two documents I'd like you to look at before we go further. The first is the one that says AFEB priorities if you haven't looked at that one already. And the second one is the last sheet on the back of the executive summary which gives a list of proposed committee members so that when the committees do break out you have some idea of which committee you're on if you don't know already.

DR. FLETCHER: And one is these is ad hoc committee. Keep in mind there are only three subcommittees now and one ad hoc.

COL FOGELMAN: And one of the things we

need to do this afternoon in addition to the other committee discussions is to try to have the committees or at least the three standing subcommittees come up with an objective for what they want to work on next year as far as strategic issues.

Now, if you recall from the last off-site -- -or from the off-site in August I was told to go back and survey the services via the preventive medicine officers to see what they thought the critical issues were for them. Okay. Take the list that you generated, go back and develop critical issues that they thought were important and then have them vote on them in a somewhat unscientific manner which is what I did.

If you'll look at the last page -- I have a matrix there -- and all of the services gave their recommendations on their top issues based on the first two pages which are the top 12 issues that they thought were important strategic issues to work on for the next year or so.

You know, using a scale of three for high, two for medium and one for low, the voting came out, the top four issues that came out were surveillance,

review of immunization programs, healthy lifestyle and behavior choices and environmental surveillance. And if you'll look -- it's environmental hazard surveillance. If you'll look at each one of those topics under the first two pages you'll see a little more detailed list of what they thought was important under those ares.

Now, the nice thing is that I think that three of those fit in very nicely with our standing subcommittees. The immunization program issue fits in with the infectious disease control committee. I did this on purpose, you know. The environmental hazards surveillance fits in with the environmental occupational health committee and the healthy lifestyle behavior choices fits in with the health maintenance, health promotion committee.

In addition, surveillance will fit under the ad hoc EPI Systems committee so the committees you set up match nicely with what the services think their priorities are.

Now, you're goal today is to take what you thought of at the off-site and what the services have said on your various issues and try to figure out exactly what approach you want to take to

working these issues over the next year. Okay. And then tomorrow at some point before we leave you'll report back on how you think you would like to approach these issues.

Now, this afternoon I think because of time we'll have the three standing subcommittees meet first and do their business and if we don't have time for the ad hoc surveillance committee to meet today you'll meet tomorrow and decide on your objectives tomorrow.

If there are other people that want to join the ad hoc surveillance committee, we need to know today or I need to know today and I can add you to the list. Or if there are people who want to have their names removed. Okay. Dr. Allen.

But we'll probably have you meet tomorrow unless you want to meet tonight sometime.

But I consider that surveillance is really going to be the most difficult issue to grapple with. And with that in mind I've asked Dr. Jones who has been working some surveillance issues for DOD to come and talk to us a little bit about where he thinks the AFEB would best be a player in this surveillance issue arena. So if you don't mind I'll

have him talk to you for five minutes about that right now before we break out into our subcommittees.

Is that clear? Have I been fairly clear on what we need to do today?

(No response.)

COL FOGELMAN: And if you don't agree with which standing subcommittee you're on for the new members, please let me know. I'll put you on another committee if I need to.

PROF BAKER: If you're on two standing subcommittees what do you do?

COL FOGELMAN: You're on two?

PARTICIPANT: Yeah, she's on EPI ad hoc and --

COL FOGELMAN: Well, EPI ad hoc is not a standing subcommittee. That one is -- those -- the people on that committee have been taken from the other three standing subcommittees. The only standing subcommittees are the top three. EPI is an ad hoc.

And that one, I can tell you will be working next year. So if you're going to be on the EPI committee and you're also on another committee

you'll probably be working two issues. So, keep that in mind with reference to time that you may have to spend on these things as well.

Okay. Bruce?

COL JONES: Well, I guess everybody must at least have been participating. I just talked --

COL FOGELMAN: Can you speak up a little bit, Bruce?

(Slide shown.)

COL JONES: I guess everybody must have been anticipating this topic other than just Colonel Fogelman and myself, Dr. Broome, of course, mentioned it and then, of course, your own top ten choices included both medical surveillance and environmental surveillance. And I think if we're going to have a military health surveillance system the AFEB could play an important role in that.

(Slide shown.)

COL JONES: I think if we're going to achieve a vision of a fully-integrated, global, seamless, peacetime deployment DOD health surveillance system as a foundation for prevention --

(Slide shown.)

COL JONES: -- it's obvious that we need to know about more than just the medical outcomes. We need to know about exposures -- hazardous exposures, and also risk factors. In trying to conceive of what is it that we're up to I've been looking for models and I think the model that seemed the most compelling was one that was developed my immediate predecessor as director of epidemiology and disease surveillance at the CHIPPM, Colonel, now retired, John Brundage. And he looked to the agent host environment TRIAD. And of course if we want to in an outbreak determine the cause of a disease or an injury we look to interactions of the host, the environment and -- or the host agent environment.

(Slide shown.)

COL JONES: And I think that serves as a model for a vision for comprehensive military health surveillance. And what we see is our TRIAD here and I think what we need to do is look at surveillance along all of the axes of that TRIAD.

Now what I've looked at most of my career is down here at the bottom, and certainly medical outcomes are important. But, again, if we're going to prevent diseases and injuries we need to know

about the hazardous exposures and personal risk factors.

The environment would include water, air, soil, food, and so forth. And personal risk factors would include demographic risk factors, immunization status, chemoprophylaxis, physical fitness, things like Colonel Kelley was talking about. And then we need to look across the entire spectrum of medical outcomes, out-patient visits, reportable diseases, hospitalizations, disabilities, deaths, and so forth. And then somehow we need to integrate all of these.

(Slide shown.)

COL JONES: Well, if we're going to do this, we clearly need to have a systematic approach to what we're doing. There are a lot of databases out there that are under utilized. At the moment we're developing the Defense Medical Epidemiology database that was funded by Defense Women's Health Research money and they see that migrating. The Army Medical Surveillance Activity has contributed to the DMED.

The DMED is a truly tri-service database and I think we need to emphasize that this needs to

be a joint military health surveillance system. To have the critical mass of minds and people that can really do this and to have the most effective system possible, I think it has to be truly tri-service. I would see these medical databases migrating into the medical outcome surveillance piece but then we need to talk, as you have listed as choice, about environmental and occupational surveillance and personal health risk surveillance.

(Slide shown.)

COL JONES: For each of those systems and for the system as a whole, I think we need to have a process in mind. And the first step of the process would be to establish objectives for each of the components of that system. And given the large number of databases that are out there, I think we need to conduct an inventory much as we did to establish the AFEB injury report. We need to do systematic inventories. And once we have those inventories then we have to evaluate each data source and each surveillance center looking at scientific quality, surveillance potential, information systems requirements for integration, and the steps in the surveillance process that have

been completed by those databases or sources.

Once we've got the inventory and the evaluation we can identify unmet data needs. We can use that inventory as an evaluation as a means of prioritizing both the analysis of data, but also incorporation into the larger elements of the system. And then we can recommend building the system in a step-wise progressive fashion.

(Slide shown.)

COL JONES: What I'd like to do is just briefly cover a couple of matrix that might be used for evaluating surveillance sources. We clearly need something that's objective. What I think of in terms of surveillance sources, here we look at the medical -- the agent or the post-outcome events -- the medical events. But we have to ask ourselves for each of these sources, out-patient visits, hospitalizations, and so forth, is it routinely collected? Is it systematic? Is it standardized? Is it population based? Has it been analyzed, interpreted and so forth?

We could come out with metrics for and checklists for quickly mapping where a data source is in this process.

(Slide shown.)

COL JONES: We could do the same thing for the environment. The agent environment access looking at food, water, air, et cetera, and specific components of those things.

Again, is it routine? Is it systematically collected? Is it standardized? Is it population based and so forth? Is there an action tied to it? And come up with checklists like this.

(Slide shown.)

COL JONES: I think when we're looking at hazards we also have to ask ourselves if we're measuring a hazard is there a health outcome? Is there acute or chronic health outcome? Is there a performance detriment associated with it and if we can measure it and there are those things, are there preventive actions?

(Slide shown.)

COL JONES: And then when we move from the data sources -- specific data sources to the overall health surveillance process, it's very important to keep the steps in that process in mind. This is an oversimplification, of course, but the first step is to have a primary source.

Is it routinely collected? Is it automated already? In the central surveillance process is the data from these primary sources being acquired? Is it analyzed? Is it interpreted? Is it disseminated? Is it out in the hands of the customers of various kinds, commanders, supervisors, policymakers, and so forth?

And ultimately, is there -- are there actions -- preventive actions associated with these databases because if there aren't actions that can come from them, there's a question as to the need to have them put money into them.

(Slide shown.)

COL JONES: And, again, I think for the surveillance centers we have to -- we can list the various types of surveillance processes and then go through our questions again. Is there a primary data source? Is it routine, automated? And check off for the central surveillance process. Is it collected, analyzed, interpreted, reported, and so forth.

(Slide shown.)

COL JONES: And I think that the Board could certainly help in this process and the types

of things that I would see the Board being able to do is establishing the criteria for incorporation of data sources into the components of the system to review the process and progress with development and to provide an evaluation of scientific quality of the data. Because if we don't have that quality, the results will be of less value in the long run.

That in a nutshell is sort of the big picture.

I'm sorry to rush through this. I had envisioned a little longer talk, but I think that that captures the elements of the types of things that I think that we need to do to have an effective tri-service, comprehensive health surveillance system.

Thank you.

COL FOGELMAN: Thank you.

(Applause.)

COL FOGELMAN: Bruce, could I ask if you could make copies of your slides for the surveillance committee tomorrow in case they want to use them?

COL JONES: Yes.

COL FOGELMAN: Thanks. I appreciate that.

I've asked preventive medicine officers and a number of other people that I know can have input to your committee discussions to stay here today, so I'll have them kind of circulating around with your committees to help. And if you have any questions I'd be happy to -- I mean, they'll be happy to answer them.

If you could all stand up, the people who have stayed around, so they can see who you are? I appreciate it. We have, I think, representatives from every service here. Okay.

Okay. So here's your pool. Take -- as I said, this list where it says "Top AFEB Priorities Recommended by Preventive Medicine Officers" this was sort of a brain storming session that we had with the preventive medicine officers one day to let them sit down and really try to define for me what they thought would be the top priorities. And then we sent the list out to the services to have it voted on. So you understand the process that went on here.

Now, there may be other issues that are very important, but they didn't shake out, at least on the top -- you know, the first discussion that we

had.

DR. FLETCHER: We had a list that we brought together from the --

COL FOGELMAN: Right.

DR. FLETCHER: -- and it was a little different. But this is the list I think we need to --

COL FOGELMAN: Right. Well, they looked at that list and they drew from that list and they also thought of things that were ongoing in the services right now which may not have come up to develop this list. So, -- yes?

PARTICIPANT: When you say they voted on them, was this simply the one preventive medicine officer from each branch?

COL FOGELMAN: I sent it to the services and they were asked to, you know, review it with their services. Now, I think in some cases that may or may not have been fully completed. Okay.

But I'm hoping that even if it wasn't and I didn't, you know, shoot this out to everybody in all the services. I depended upon the preventive medicine officers to do that for me. But even if it didn't get to everyone that they have a pretty good

feeling for what the critical issues are for their services.

Am I saying anything wrongly here? Can the services corroborate what I just said? Yes?

PARTICIPANT: Yes.

COL FOGELMAN: No?

PARTICIPANT: Yes.

COL FOGELMAN: Okay. All right.

DR. FLETCHER: Ken?

DR. WARNER: If I could just ask a question. It really surprised me in the rankings and I don't know if this -- is mental health something that somebody else worries about? Because it strikes me as a world health organization just came out with their new report saying, you know, the greatest cause of disability adjusted life year -- now, maybe everybody in the military is well adjusted mentally, I don't know.

I was just really surprised to see the uniform, you know, low rating here.

COL FOGELMAN: Well, I think that -- it's not that they think that mental health is a -- is not an issue. One of the issues that was stated to me and I'll let the services talk to this as well,

was that maybe they didn't feel that on the board we had that much expertise to evaluate some of the mental health issues. And there already some -- there are some --

(Cross-talk.)

COL FOGELMAN: -- some ongoing process I know already in DOD to look at some of these issues, but I know the services need to get their say in here.

Trueman?

CDR SHARP: Yeah, I think that all the topics reviewed as important issues, but I thought our task was what were the priorities and what would they most like to see the AFEB tackle.

COL FOGELMAN: Right.

CDR SHARP: I don't think this is saying that -- you know, they don't think mental health is important. It was rather, what do they want the AFEB to --

COL FOGELMAN: Right.

CDR SHARP: -- deal with first.

COL FOGELMAN: Exactly. Yes, Dr. Gwatlney?

DR. GWALTNEY: I think any effective health promotion program you're going to have too should

deal with mental health. So I think that's incorporated in that.

DR. FLETCHER: Yeah, that goes sort of without saying. But it really should be said.

COL FOGELMAN: Right. Right.

DR. LaROSA: I just have a comment on that and I'd like a response of the preventive medicine officers. I guess I'm reacting along with Cannon and with Jim too who hasn't spoken out on this, but we chatted briefly before, when you look at the data that was presented in this, the national mortality profile, and you look at what's come out about Gulf War and everything, what you see is a lot of unspecified symptoms in Gulf War which relate to mental health issues. And in this you see some nasty rates for suicides and homicides, and abuse and things like that. And I agree with my colleague, Dr. Gwaltney, that it is a part of a total fitness.

But I was surprised, too, to see it down at the bottom of the pile given all of the data that seem to be emerging these days. Commentary, please? Sir?

MR. LITTMAN: (Off mic.) I can tell you

the terms of the -- Rod Littman -- in terms of the Bosnia deployment, the early deployment of significant numbers of mental health professionals assigned to a division of combat stressed teams the -- around 2,500 to 3,000 people were given a pre-deployment psychological survey. We've seen in R&D teams to assess mental health during the deployment. We have a fairly extensive post-deployment mental health screening. Mental health the prevention, the early intervention, the treatment is a very, very big issue today and is part of the entire comprehensive theater for balanced program.

So I don't -- in that respect it hasn't been short changed.

LT COL EGGERT: I'd reiterate that for the Air Force currently in operation Desert Focus. This is Lieutenant Colonel Eggert. We're continuing the same types of surveillance activities to include mental health surveillance referral and follow up and there are some very important initiatives in suicide prevention going on in the Air Force currently. So I think we just felt that there were other venues that were approaching the mental health issues.

DR. FLETCHER: Dr. Allen?

COL FOGELMAN: That's okay. Who was first? Dr. Broome?

DR. BROOME: Just as a follow on, I'm just interested as to whether the other venues have an epidemiologic focus? I think it's very commendable, that a lot of these activities are happening. I'm curious as to how well they're being evaluated and monitored?

DR. WALDMAN: I think that's -- at least personally -- I think that's why the surveillance rose to the top because we frankly don't have measures for lots of these program areas. And without a surveillance system which is comprehensive captures many events of interest. You ask that about many of these program areas and we're not sure we have good numbers.

At least we're uneasy to cite numbers in many of these areas and it's sort of the fundamental thing. Give us a surveillance system and we really can decide what's our big problems --

COL FOGELMAN: Right.

DR. WALDMAN: -- or less important --

COL FOGELMAN: It's sort of like build a

surveillance system and the problems with come. I mean, we'll see what the real problems are.

DR. ALLEN: To use a well-worn phrase, I think we're at early or in the middle of the paradigm shift here. I mean, if you look at what the AFEB was even five years ago, much less 15, it was predominantly infectious diseases. And we are and have been changing that very forcibly.

I mean, look at the composition of the Board today. I think mental health is one issue specifically that probably hasn't yet come to the fore as something that the Board can and should be involved with. But I think taking the broader approach as has just been discussed in the last two minutes where we look at additional surveillance information, epidemiologic studies, and the evaluation of programs that are put in place, we're going to find that we have to address that issue and will get involved with it in -- in multiple ways.

COL FOGELMAN: Right. I agree.

DR. FLETCHER: Let me say a couple of things before we adjourn. Preventive Services we decided to kick this into committee because there's still some work that needs to be done over this

week. We shortened the agenda so we would deal with this in our committee specifically. And to second what Jim said, I think really we are coming around to more a diffuse board based on the original chartered subcommittees, the three we have now as opposed to chronic disease which was really predominant 10, 15 years ago. In the last five years we're getting a better balance and all these issues, I think, will sort out with our committee work.

Committee I think when we break out, there are about four things we need to begin to have a response for, that's G6PD. I don't think we can have a response, but we need -- these are questions for the Board and the subcommittee. The hepatitis A and the -- the adenovirus. We need a response there.

I think to work towards some sort of level of response sort of as we came out eventually with the sickle cell trait. So we need to have, as the Board, as evolving to not an instance of have a response but we're asked to have a -- to respond to a question. So we don't have to have that necessarily late today or tomorrow, but I think work

towards that. And we will do the same in the clinical preventive services in our committee.

COL FOGELMAN: Dr. Sharp?

CDR SHARP: Sorry to regress here, but to go back to this, I just want to make a couple of other points. At least the way I did this in the Marine Corps was to ask a number of the senior medical people at the Marine Corps and so a couple of comments that I'd make are that along the lines of this paradigm shift I think a lot of them have a preconception based on their past experience of what the AFEB does. And so -- so for example, on excession standards, and that is a big, big issue. And a senior medical person said, well, yeah, it's big issue, but what could the Armed Forces EPI Board do with that?

I mean, we saw a great presentation this morning about the role of the epidemiology in that. So, I think they may be caught in this paradigm shift to some extent themselves.

The other thing is that they are -- some of these are, you know, orthopaedic surgeons and so forth and aren't epidemiologic minded and so I -- what I tried to do was say, you know, just let the -

- so your medical people -- so, you know, based on what you do everyday, what do you see as important and this is what they said. So --

COL FOGELMAN: So, any other questions or comments before we break out?

(No response.)

COL FOGELMAN: I think if the committees can get through, at a minimum, trying to decide on their approach to these particular issues today that we'll be in good stead. Then tomorrow morning we'll make time for the surveillance committee to meet at some point. Or, if you wish to meet tonight it would be even better. But I'm not going to force you to meet tonight. And it would probably have to be back at the ranch -- at your hotel.

But I think that's a key committee and one that will need to work this year. Surveillance really came out the highest of all the -- all the issues that were addressed.

So what I think we'll do, we have the warroom, if you want to use it, but it might be better to break out in here. If we could just divide into four corners or let's say -- I mean three corners. Three corners. Infectious disease

committee down here, environmental and occupational health committee up here, and health maintenance promotion at the table, how does that sound? Somewhere at the table. Does that sound reasonable?

And then I'd like the preventive medicine officers to -- to -- you know, the committees that they think they have the most input for. I know Dr. DeFraites has some input on the adenovirus issue. And then maybe circulate to the other committees and see if you can provide them with some help or input there as well.

I haven't planned anything for this evening. Maybe I should have, but I figured everybody would be pretty tired tonight and so I didn't plan a reception or anything. If there's any real -- does anyone really want to have a group dinner or anything like that? Do you feel that that's something you'd like to do tonight?

PARTICIPANT: Maybe you could tell us where there is near the beautiful downtown Holiday Inn that you would recommend that we eat?

COL FOGELMAN: Yeah, I can't. I'm not from here -- this area. But there may be --

Elizabeth will take care of it. Do you

know the area?

(Cross-talk.)

COL FOGELMAN: Okay. Dr. LaRosa said she knows a lot of places near the Holiday Inn.

DR. LaROSA: No, not near. In the Bethesda, Rockville --

COL FOGELMAN: Oh, that's a whole different dining room.

What we'll do -- if I could just make one more comment, once you feel like you've completed your work tonight, I think we'll just say, you can feel free to leave. If you don't have transportation, check with me and we'll see if we can't set something up.

But I think we'll plan on working till five and if the surveillance committee can get together tonight, then all the better, but if not --

PARTICIPANT: Three of those members are not here.

COL FOGELMAN: Okay. Well, we still need to meet with those that are.

(Cross-talk.)

(Whereupon, at 4:05 p.m., the conference was adjourned to reconvene on Friday, December 13,

1996 at 8:00 a.m.)